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VARIETIES OF BODILY EXPERIENCES.
NEURAL AND BEHAVIORAL EXPLORATIONS IN THE BORDERLANDS OF BODY AND SELF

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VARIETIES OF BODILY EXPERIENCES

Neural and behavioral explorations in the borderlands of body and self

To my parents,
and to the memory
of my nephew.

TABLE OF CONTENTS

INTRODUCTION

Our body is the most privileged medium we possess to experience our self. Our self is bound to the body and we feel rooted to it. The boundaries of our body, set by bone and flesh, constrain and provide the space where our self can reside. Experiencing our self transcending these boundaries requires the greatest stretch of the imagination. Likewise, we can hardly imagine that what lies within these boundaries may be experienced as non-belonging to our self, may be attributed to someone else, or may fade away from awareness and become non-existing. On the other hand, it may sound almost delusional that beyond these boundaries we could still experience physically missing body parts. However, the experience of the body and the self as two inseparable entities in unison can be, under certain circumstances, shaken. Following brain anomalies, for instance, the spatial extent of the physical and the phenomenal bodies may no longer match. This informs us that the unified experience of having a body – something that most of us would find self-evident - is the product of assorted and complex neuronal processes. In my thesis, I shall provide both a neural and phenomenological account of the borderlands of the experience of having a body: the bodily self.

Study 1 (Saetta et al., 2020a) examined the case of Body Integrity Dysphoria (BID), where a limb can be experienced as nonbelonging despite healthy, ordinary anatomical development and integrity of sensory and motor functions. BID is indeed a rare yet non-psychotic condition characterized by dissatisfaction with the own body boundaries, often leading to the desire for amputation of one or several limbs. Most BID individuals use crutches or wheelchairs to align the actual body and the desired one (First & Fisher, 2012). In BID individuals, a body lacking a limb is apparently better suited to host their self. The discrepancy between the actual and desired body may be so distressing that affected individuals might engage in hazardous behaviors, i.e., self-amputation (Sedda & Bottini, 2014). For a long time, BID was conceptualized as an internet-induced madness or a paraphilia, and not considered worthy of being studied. The new release of the 11th Revision of the International Classification of Diseases (ICD 11) proposes to define BID as a "disorder of bodily distress or bodily experience". This new definition as an "official illness" prompted us to uncover the neural correlates of this "new" condition. Despite the rarity of BID, in study 1 we gathered gray matter density and functional connectivity data from 16 affected men with a very homogenous manifestation of BID, i.e., the long-lasting and exclusive desire to have the left leg amputated. Sixteen healthy men functioned as controls. This was by far the largest neuroimaging study of the condition, considering that previous investigations have included only a small number of individuals with an amputation desire targeting different limbs. Having a homogeneous and relatively large sample allowed us to delineate the anomalies of the specific brain networks that may be associated with the lack of ownership over a single limb and the desire for its amputation. We found that the feeling that a limb does not belong is tied to reduced functional connectivity of the area containing the primary sensorimotor representations. Furthermore, a key area for representing the body shape, the right superior parietal lobule, was atrophic in BID individuals. Noteworthy, the more atrophic this area, the more BID individuals simulated being amputees to solve the mismatch between the actual and desired body. Our findings suggest that the desire for amputation in BID individuals may be related to specific anomalies in brain architecture. In the wake of the release of ICD-11, our study was particularly relevant, as this edition of the ICD will turn a "fad" into an officially recognized mental disorder.

Study 2 (Saetta, Michels, & Brugger, under review) explored the neural networks of the "neuropsychological counterpart" of BID, i.e. somatoparaphrenia: the denial of the ownership of a paralyzed limb in brain-damaged patients (Gerstmann, 1942). While the least common denominator of BID and somatoparaphrenia is the feeling that a limb doesn't belong (Ramachandran & McGeoch, 2007), two main aspects separate these two fundamentally different conditions. First, while BID is a developmental disorder originating in early childhood, somatoparaphrenia represents an acquired condition. Moreover, BID individuals are not delusional because they recognize the disowned limb as still part of their physical body. Instead, somatoparaphrenia is characterized by a productive component, i.e., the misattribution of the paralyzed limb to someone else (Bottini et al., 2002). In this respect, somatoparaphrenia could be seen as the "filling in" of the phenomenal body lacking a limb with the presence of that of someone else (Brugger & Lenggenhager, 2014). Study 2 was designed to uncover the neuronal processes related the productive component of somatoparaphrenia. We implemented new functional magnetic resonance imaging (fMRI) methods in the context of somatoparaphrenia and studied a right-hemisphere brain-damaged patient with no premorbid neuropsychiatric disorders claiming that his left plegic hand belonged to his mother. In the scanner, this patient was asked to imagine the mother moving the hand, and, in control conditions, to imagine moving the right and the left hands. Our findings link the productive component of somatoparaphrenia to the activation of a key area for the multisensory integration of the affected limb: the pars opercularis of the right inferior frontal gyrus. In a separate resting-state fMRI experiment, recruiting an additional 21 controls, we reconstructed the functional connectome of the somatoparaphrenic patient and identified its alterations in reference to that of the controls. We found that the activation of the pars opercularis of the right inferior frontal gyrus was coupled with the deactivation of the left fronto-parietal mirror network. Pioneering application of the fMRI technique for the investigation of the neural correlates of somatoparaphrenia revealed that the limb's misattribution might be related to both a disturbance of multisensory integration in the brain and a disturbance in interhemispheric communication.

Study 3 (Saetta et al., accepted for publication) focused on another aberrant experience of disunity between the body and the self, characterized by the impression that one's own body or body parts have ceased to exist, i.e., asomatognosia (Critchley, 1953). Typically, only one half of the body, more often the left, contralateral to a lesion of the right hemisphere, is affected. Pure asomatognosia is confined to the somesthetic modality, but the disorder may extend to the visual modality whereby the affected body parts are no longer visible (Arzy et al., 2006; Magri & Mocchetti, 1967). In study 3, we reported the case of a patient affected by pure hemisomatognosia that followed the surgical removal of a meningioma in the right atrium. We elaborated on the rigorous definition of the disorder. Accordingly, we presented the template for a structured clinical interview useful for the differential diagnosis of asomatognosia, which allows for the characterization of its core symptoms and their separation from associated symptoms. In previous literature, such separation has not been made with the rigor it would deserve. Asomatognosia has even been referred to as a disorder of ownership (Feinberg et al., 2010). Furthermore, we presented and shared a computerized task that facilitated the capture of phenomenological elements of a case by chronometric means. It is a limb laterality task requiring the mental rotation of limbs and tailored such that objective, limb-specific impairments can be matched with a patient's subjective report. In the patient, we found that the mental rotation of limbs seemed to be impaired explicitly for *left*-sided limbs and more so for feet than for hands, especially for postures requiring the evocation of motor rather visual limb representations. This pattern of results reflects the phenomenal characteristics of this individual case, i.e., a *left*-sided hemiasomatognosia confined to the *somesthetic* modality and more enduring for the *lower* compared to the upper limb.

While studies 1-3 (Saetta et al., 2020a; Saetta, Michels, & Brugger, under review; Saetta et al., 2020b) presented aberrant experiences where the self is *not* permeating the entire space delimited by the bodily boundaries, studies 4-5 (Saetta et al., 2020c; Saetta et al., 2018) examined the experience of self as extending to the extracorporeal space. What I refer to here are phantom limb sensations. Experienced by almost all amputees, phantom limb sensations represent the persistence of the missing limb as if it were still present, despite its amputation (Brugger, 2006). The "ghostly" aspect is explained by the postural and motor nature of these sensations. Indeed, amputees do no visually hallucinate the missing limb, but they can still perceive it as if it occupied a precise position in space. Phantom limbs are felt to have a specific size, can be moved or not, and can even generate painful sensations. Also located in extracorporeal space are the prostheses, which are of physical matter that can be felt as an extension of the self, depending on their interaction with the phantom limb. Indeed, some peculiarities in an individual's phantom limb experience may offer unique insights into how prostheses may be optimally embodied, i.e., incorporated in the self and controlled and felt as one's own limb. However, this interaction between mental and physical matter has been largely neglected in previous literature.

In Study 4, (Saetta et al., 2020c) we developed and shared with the scientific community an extensive assessment of the individual differences in phantom limb sensations via a set of both established and custom structured clinical interviews. We recruited 15 upper limb amputees. The self-reported measures were integrated with a multimodal dataset combining motor information of the residual limb, namely surface electromyography and accelerometry, with gaze, from three experiments. Twenty-nine physically intact (normally limbed) participants were also tested as controls. Experiment 1 of study 4 examined the eye-phantom movements coupling during a classic visually-guided pointing task with real and imagery pointing movements. Amputees aimed at squares of different dimension with the tip of a pen, imagining to use their phantom limb. Experiments 2-3 of study 4 were designed to objectively measure the reactions of the phantom limb when its location and physical matter co-existed in space. Amputees repositioned the phantom from a starting to an end-point in the presence of hindering physical matter, an "obstacle", in between these starting and end points. Since prostheses are also physical matter, understanding the way each individual experiences the phantom limb and whether it tolerates or shuns physical matter, could prove a major achievement for the design of prostheses that can be truly integrated into the bodily self. In Study 5 (Saetta et al., 2018), we proposed new labels for these two fundamentally different modes of phantom limb experience. *Obstacle shunning* refers to the experience that phantom limbs fade away or "bend back" once their phenomenal space overlaps that of physical matter. Alternatively, *obstacle tolerance* refers to the experience that the phantom limb maintains its ghostly existence once brought into superposition with physical matter. In the case of obstacle shunning, phantom properties adhere to the law of impenetrability of physical matter. In the case of obstacle tolerance, they do not.

In Study 5, we characterized obstacle shunning and obstacle tolerance with quantitative methods. Twelve lower limb amputees (6 obstacle shunning, 6 obstacle tolerance) and 14 controls were tested with a novel apparent motion perception task with human body parts as stimuli. We looked at whether amputees' perception of a phantom limb and its interaction with the environment in everyday situations could be related to performance in this task. Our results suggest that this seems to be the case. In particular, we showed that lower limb amputees with obstacle shunning were more likely to report the illusory percept of the leg to move through the object. On the other hand, amputees with obstacle tolerance were more likely to perceive a leg to go around an object, suggesting that, in these amputees, the phantom limb representation imposes the same constraint as an intact limb does. These results imply that the presence of obstacle tolerance might predict a better prosthetic fit, which is in line with previous literature describing a positive correlation between the vividness of a phantom and the embodiment of a prosthesis. Our results encourage use of this task to explore the relationship between the body and the self on an implicit level. Currently, assessments of the disturbances of the bodily self are mainly based on self-report and explicit measures.

The aim of the present thesis was twofold. On one hand, I wanted to shed new light on the neural and behavioral aspects underlying the bodily self. On the other hand, I designed tools for the clinical assessment and the experimental investigation of its disorders.

The presentation of the 5 studies will be followed by a general discussion where I will report the rationale, the method, the findings and their implications, as well as the limitations of these studies. Together, the data will illustrate the multifaceted nature of the bodily self and tentatively outline how contributing factors, from neurological to social, can be mapped to the brain and be reflected in behavior, and how they may be employed for both clinical and research purposes.

STUDY 1. BODY INTEGRITY DYSPHORIA

Neural correlates of Body Integrity Dysphoria

By **Gianluca Saetta**, Jürgen Hänggi, Martina Gandola, Laura Zapparoli, Gerardo Salvato, Manuela Berlingeri, Maurizio Sberna, Eraldo Paulesu, Gabriella Bottini, Peter Brugger

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ABSTRACT

There are few things as irrefutable as the evidence that our limbs belong to us. However, persons with body integrity dysphoria (BID) deny the ownership of one of their fully functional limbs and seek its amputation. We tapped into the brain mechanisms of BID examining sixteen men desiring the removal of the left healthy leg. The primary sensorimotor area of the to-be removed leg, and the core area of the conscious representation of body size and shape (the right superior parietal lobule, rSPL) were less functionally connected to the rest of the brain. Furthermore, the left premotor cortex, reportedly involved in the multisensory integration of limb information (Blom et al., 2016; Ehrsson et al., 2005b; van Dijk et al., 2013) and the rSPL were atrophic. The more atrophic the rSPL, the stronger the desire for amputation, and the more an individual pretended to be an amputee by using wheelchairs or crutches to solve the mismatch between the desired and actual body. Our findings illustrate the pivotal role of the connectivity of the primary sensorimotor limb area in the mediation of the feeling of body ownership. They also delineate the morphometric and functional alterations in areas of higher-order body representation possibly responsible for the dissatisfaction with a standard body configuration. The neural correlates of BID may foster the understanding of other neuropsychiatric disorders involving the bodily self. Ultimately, they may help us understand what most of us take for granted, i.e. the experience of body and self as a seamless unity.

INTRODUCTION

Human beings commonly experience their bodily self as laying within clearly circumscribed borders defined by biological and societal norms. Paradoxically, in persons with BID the desired amputation would make those concerned with the condition "*feel more complete*", and those having reached an amputated state only regret not having realized it earlier (Noll & Kasten, 2014). Two behavioral features are almost invariably associated with the condition, albeit to varying degrees: (i) an erotic attraction to (lower limb) amputees and (ii) the habitual simulation of the desired body state by using crutches or wheelchairs ("pretending behavior") (First & Fisher, 2012). Despite the rarity of this condition, we succeeded in recruiting sixteen men who all desired an amputation of specifically and exclusively the left leg. None had any history of major psychiatric or neurologic disorders. BID participants were compared to sixteen healthy control men matched for age and formal education. Pinpointing the differences in the functional and structural architecture between BID individuals and control persons' brains provided the unique opportunity to reveal the neural networks involved in the sense of ownership of a limb as an integral part of the body. Moreover, it allowed us to identify the candidate brain areas underlying the satisfaction of possessing a determined body configuration. In particular, in BID individuals we explored: i) alterations in intrinsic functional connectivity in cortical hubs (i.e., small multimodal areas reached by many functional connections disproportionate to their spatial extension (Buckner et al., 2009; Rubinov & Sporns, 2010; Sporns et al., 2007); ii) structural atrophies or hypertrophies in the functionally altered regions as well as in other specific candidate regions (Blom et al., 2016; Hilti et al., 2013). Alterations in functional connectivity and the concentration of gray matter were related to the self-reported characteristics of an individual's amputation desire, as carefully assessed in a clinical interview.

RESULTS

Cortical hubs with reduced intrinsic functional connectivity in BID compared with controls were the right paracentral lobule (rPCL), the rSPL, the pars orbitalis of the left inferior frontal gyrus (lIFGOrb), and the left inferior temporal gyrus (lITG). Results are shown in Figure 1 and Table 1. The areas with a reduced concentration of gray matter in BID compared with controls were the rSPL, the left premotor cortex (lPMv), and the lIFGOrb. Results are shown in Figure 2 and Table 1. The concentration of gray matter in the rSPL negatively correlated with the strength of the desire for amputation (Pearson's correlation coefficient, $r_{(14)} = 0.51$, $p = 0.01$) and the pretending behavior (Pearson's correlation coefficient, $r_{(14)} = 0.62$, $p = 0.01$, see also Figure 2), as assessed by the respective subscores at the Zurich Xenomelia Scale (Aoyama et al., 2012).

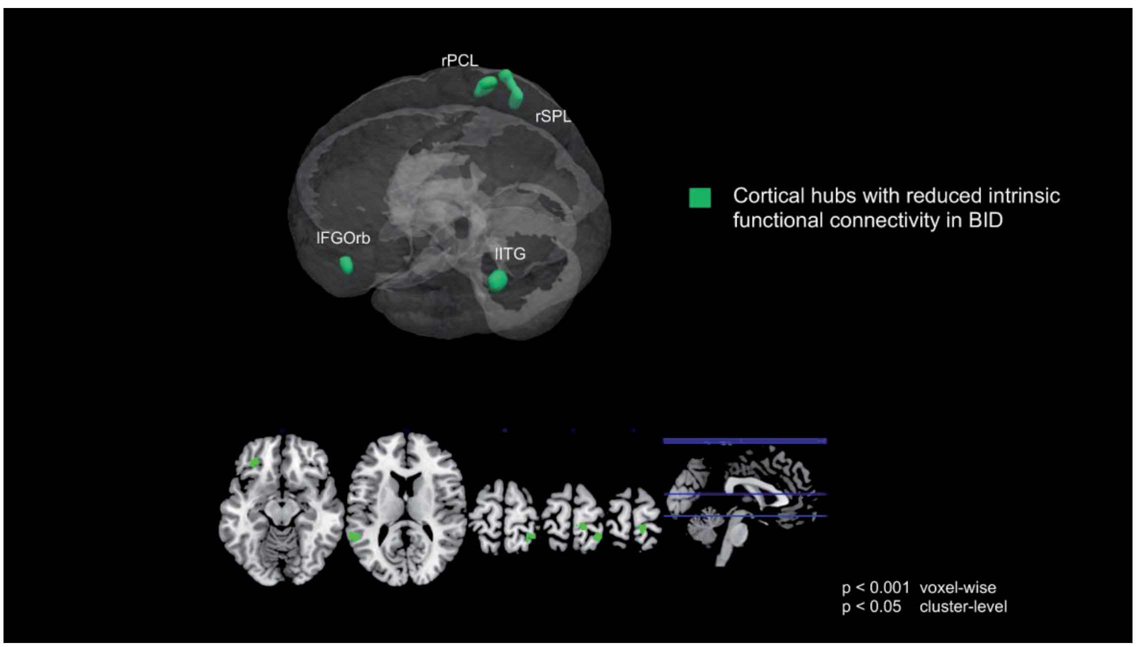

Figure 1. Reduced intrinsic connectivity of cortical hubs in BID. Results are extracted at p < 0.001 voxel-wise and p < 0.05 cluster level (not corrected). lIFGOrb, pars orbitalis of the left inferior frontal gyrus; rPCL, right paracentral lobule; rSPL, right superior parietal lobule; lITG, left inferior temporal gyrus.

Table 1. Reduced intrinsic connectivity of the cortical hubs, atrophies, and hypertrophy in BID.

Brain regions (BA)	MNI coordinates							
	Left hemisphere				Right hemisphere			
	x	y	z	Z-score	x	y	z	Z-score
Reduced intrinsic connectivity ofthe cortical hubs in BID								
Inferior Orbitofrontal Gyrus	-32	36	-12	4.23				
Paracentral Lobule					10	-38	78	4.04
Superior Parietal Lobule					22	-52	60	3.79
Inferior Temporal Gyrus	-60	-44	16	4.16				
Atrhopies in BID								
Inferior Orbitofrontal Gyrus	-36	36	-9	6.05				
Precentral Gyrus	-38	2	34	5.63				
Precentral Gyrus	-50	2	27	4.82				
Superior Parietal Lobule					39	-56	57	6.5
Hyperthropies in BID								
Middle Temporal Gyrus	-60	4	-21	6.3				

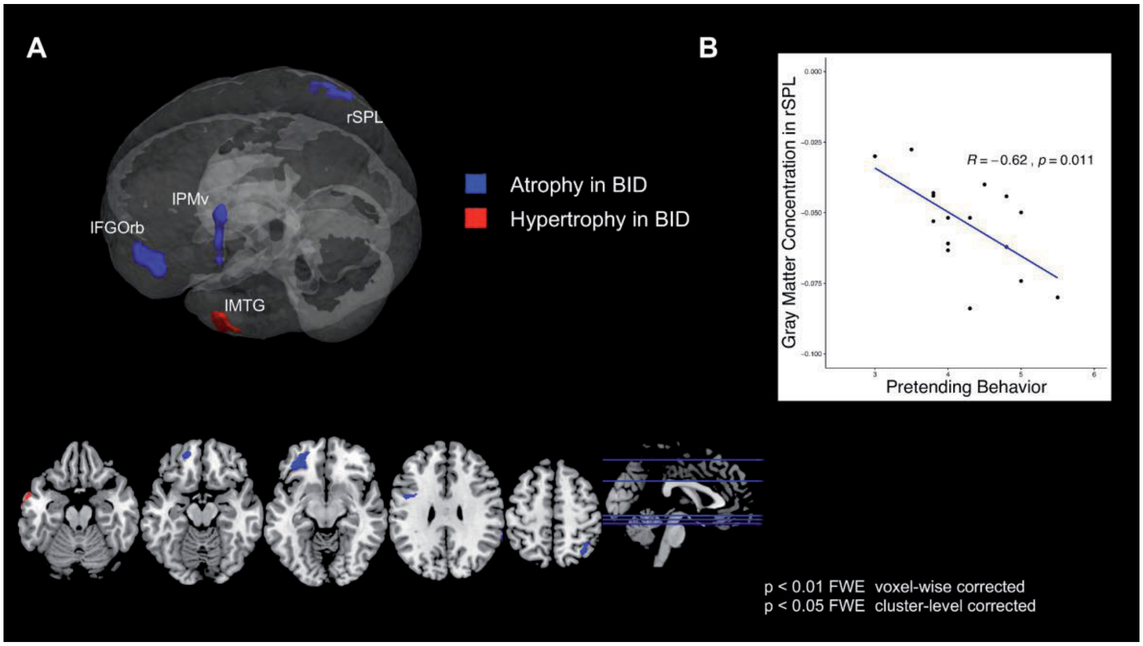

Figure 2. Atrophies and hypertrophies in BID. A) Atrophic and hypertrophic areas in BID. Results are extracted at p < 0.01 FWE voxel-wise corrected and k > 25. (B) Scatterplot of the correlation between the concentration of gray matter in the rSPL at [X = 39, Y = - 56, Z = 57] and the pretending behavior in BID individuals. On the y axis, the contrast values (reduced concentration of gray matter in BID individuals compared to controls) are reported. lPMv, left ventral premotorcortex; lMTG, left middle, temporal gyrus; IFGOrb, inferior frontal gyrus; pars orbitalis; rSPL, right superior parietal lobule.

DISCUSSION

The right paracentral lobule (rPCL), which houses the primary somatosensory representation of the affected left leg, showed a reduced intrinsic functional connectivity to other cortical regions. Remarkably, no *structural* alterations were evident in the rPCL, which is in line with a normal neurological status examination, specifically showing unimpaired tactile and motor functioning of BID individuals' left leg. The rSPL showed both reduced intrinsic functional connectivity and concentration of gray matter. The absence of any neurological deficits or BID-related symptoms for the right leg and both the upper limbs suggests a specificity of these alterations for the desired removal of the left leg. Our results support the view that the distressing feeling of non-acceptance of one's limb in BID might ensue from a discrepancy between preserved projections of somatosensory inputs from the limb to the respective primary cortical areas, and an impaired representation of the body at the highest level of integration, the so-called *body image* (McGeoch et al., 2011). That is the representation of the size, shape and physical composition of the body, i.e., 'the conscious body image' (Gadsby, 2019; Longo, 2015; Longo et al., 2010). The rSPL was previously identified as a critical hub for the body image (McGeoch et al., 2011; Ramachandran et al., 2009). Specifically, a MEG study showed that in BID individuals, the tactile stimulation of the to-be removed limb was accompanied by reduced activation of the rSPL (McGeoch et al., 2011). Likewise, a surface-based morphometry investigation reported a reduced thickness of rSPL in association with BID (Hilti et al., 2013). Body image arises from the integration of multiple sensory inputs (i.e., visual, tactile, proprioceptive, vestibular, and re-afferent motor signals). It is thought to be scaffolded by the activity of distributed neural networks whose integrity is responsible, on a phenomenal level, for an individual's perception of his or her own body as coherent and unitary (Longo et al., 2010). A central region for multisensory integration, the lPMv (Ehrsson et al., 2005b), was found atrophic in the BID individuals examined here. The lPMv binds together visuomotor and tactile information about a limb through its anatomical connections to frontoparietal areas (Rizzolatti et al., 1998). A specific role of the lPMv in multisensory integration and limb ownership was already suggested in previous studies on BID (Blom et al., 2016; van Dijk et al., 2013). BOLD activity in the lPMv was decreased in 5 individuals with BID during the touch of the desired-to-be removed compared to the accepted limb (van Dijk et al., 2013). Atrophies in the lPMv have been described in a subsequent study(Blom et al., 2016).

Previous studies, cited above, were preliminary in that a small number of BID individuals with an amputation desire targeting different limbs had been recruited.

Moreover, these studies investigated separately either functional characteristics (McGeoch et al., 2011; van Dijk et al., 2013), connectivity (Hänggi et al., 2017) or morphometry (Blom et al., 2016; Hilti et al., 2013) of BID individuals' brains. The novelty of the present approach consists in the combination of morphometric (gray matter density) and functional connectivity analyses within one, relatively large and homogenous sample. The results produced by previous studies also did not survive conservative statistical thresholding. Here, results were extracted at $p < 0.001$ uncorrected at the voxel-wise level and $p < 0.05$ at the cluster-level to identify the cortical hubs presenting altered functional connectivity in BID (listed in Table 1 and displayed in Figure 1). Regional GM reductions in BID were explored by applying the most conservative thresholding method available in SPM ($p < 0.05$ FWE voxel-wise corrected) coupled with a cluster-extent threshold of $k > 25$ to further exclude spurious findings. The results are listed in Table 1 and displayed in Figure 2. Our findings, combined with the integration of results from previous studies, allow the formulation of an evidence-based, comprehensive model of the neural networks implicated in BID. According to this model, BID might be characterized at a neural level by i) insufficient anchoring of limb representations as suggested by the lack of intrinsic functional connectivity in the rPCL, ii) a deficit in multimodal integration, as indicated by structural anomalies of the lPMv and rSPL, iii) altered body image in the rSPL, reflected by both functional and structural abnormalities of this region.

Body image in the rSPL has been proposed to be genetically determined(Ramachandran & Hirstein, 1998). A proof of concept might be the observation of phantom limb sensations in amelia, i.e., the phenomenal existence of a limb despite its physical absence in humans born without the respective limb (Brugger et al., 2000). It was previously shown that an amelic individual imagining or executing phantom limb movements activated no primary sensory and motor areas but the rSPL

(Brugger et al., 2000). BID and amelia might share a common altered developmental mechanism responsible for the discrepancy between physical and phenomenal body states (Hilti & Brugger, 2010). This perspective becomes more compelling when taking into account our finding of an association between rSPL architecture and the strength of the amputation desire on the one hand and inclination to pretending behavior on the other hand. Specifically, the more atrophic rSPL, the stronger the desire for amputation and the more a BID individual would mimic the status of an amputee. Alteration of the rSPL might be the neural substrate of a BID individual's unusual body image. The pretending behaviour could represent the attempt to solve the mismatch between the experienced and the desired body. The transient alleviation of the desire for amputation obtained by binding up the leg or sitting in a wheelchair might stem from the alignment of the actual visual information about a temporary amputated body state and the individual's body image that lacks a limb. Accordingly, Stone et al. (2018) induced in BID individuals the illusory experience of the affected limb to fade off from visual awareness. This gave them instant relief from their symptoms, if only transiently. Other evidence that body image is built up at a very early stage of development, is that the experience of BID typically lasts as long as an individual can remember. The characteristics of the desire for amputation (i.e., the affected limb, the exact demarcation line etc.) usually remain stable across a BID individual's lifespan. Pretending behaviour might thus correspond to acting out a possibly innate, individually shaped body image.

Oddo et al.(2018) recently presented BID individuals and controls with morphs depicting either the observer's actual or amputated body. In that study, multivariate statistics using machine learning were able to discriminate between a BID group and a control group based on the BOLD signal in the rSPL. In line with previous reports (Blom et al., 2017), BID individuals rated pictures of amputated bodies as more pleasant and sexually arousing than those of intact bodies. Taken as a whole, these findings might suggest an interdependence between a person's bodily self and her sexual orientation along the spectrum of bodily appearance. From a neural point of view, Ramachandran et al. (2009) proposed the possible existence of a genetically-determined cortical template of body image hard-wired into the rSPL. Such a template would shape the connections within the limbic system, promoting an individual to be attracted erotically towards body shapes that match those contained in this template. Therefore, donkeys prefer other donkeys as sexual partners, and humans prefer other humans. BID individuals, whose body image lacks a limb, prefer amputees. Indeed, the majority of BID individuals with a desire for lower limb amputations are also attracted to lower limb amputees (Ramachandran et al., 2009). In line with Ramachandran's intuition, we found that in persons with BID the pars orbitalis of the left inferior frontal gyrus (lIFGOrb), which belongs to the limbic system, showed both reduced intrinsic functional connectivity and concentration of gray matter. Future studies should tap into the cerebral networks for body image and erotic attraction to bodily appearance, examining in more detail the possible relationship between the rSPL, the lIFGOrb, and the limbic system.

The empirical approach taken in the present study illustrates that the bodily self critically depends on the functional connectivity of the limb primary sensorimotor area rather than its structural properties. However, at higher levels of bodily representation, both functional connectivity *and* gray matter characteristics of multimodal integration hubs seem to be necessary for a healthy binding of body and self. Only a smooth interplay between low level and high level bodily processing make us feel that single limbs belong to our body as much as to our self. And only such integrity between body and self will guarantee satisfaction in both personal and social life. In this respect, an old, but almost forgotten, wisdom about the bodily self regains appreciation: "Body image is a social phenomenon" (Brugger & Lenggenhager, 2014; Schilder, 1935).

Our findings suggest that the desire for amputation in BID individuals might be accounted for specific anomalies in brain architecture. Such a view complements previous conceptualizations of BID as a paraphilia or an Internet-induced madness (Brugger et al., 2016). The upcoming release of ICD-11 proposes to define BID as a "disorder of bodily distress or bodily experience". We have outlined here the neural correlates of this "new" condition.

The empirical approach taken in this study is correlational in nature. The neuroimaging methods used here do not allow any inferences on causality. However, facing graphical depictions of a relationship between cortical structure and behaviour, the vector of causality is reportedly biased in a brain-to-mind direction (Brugger et al., 2018). This holds for laypeople and academics alike and underlines the necessity of considering nonlinear interactions of biological, psychological and social factors underlying BID. An integrative, crossdisciplinary view might have promising implications for the understanding of neuropsychiatric disorders such as BID, and will ultimately allow refined definitions of diagnostic criteria.

METHODS

Participants

Sixteen men who all desired an amputation of the left leg were recruited from an advertisement posted on the following website http://www.biid-dach.org/. Eight BID individuals were scanned at the Department of Neuroradiology of the University Hospital of Zurich(Hilti et al., 2013). The other eight BID were scanned at the Neuroradiology Department of the "ASST Grande Ospedale Metropolitano Niguarda" of Milan. Their ages ranged from 28-67 years with a mean of 44.38 years and a standard deviation (SD) of 12.32 years. Their years of education ranged from 13-18 years (mean = 16.06 years, SD = 2.28 years). Table 2 offers an overview of participants' demographic variables and the characteristics of their amputation desire according to an established scale, the Zurich Xenomelia Scale(Aoyama et al., 2012) (see below).

The control group consisted of sixteen healthy men. They were pair-wise matched to the BID individuals by sex, age (range = 31-62 years, mean = 44.81 years, SD = 8.82 years, paired t-test: $t(15) = -0.11$, $p = 0.915$), years of education (range = 8-18 years, mean = 15 years, SD = 3.38 years, paired t-test: $t(15) = 1.10$, $p = 0.28$). All participants provided written informed consent to take part in the study. The study was approved by the Ethics Committee of the University Hospital of Zurich and by the Ethical Committee Milano Area C. The study was run in compliance with the guidance provided in the Declaration of Helsinki (1964).

Clinical assessments and questionnaires

All participants were screened for physical and mental health in standard neurological and neuropsychological examinations and a psychiatric assessment, which included a series of validated instruments and, for the participants with BID, a 2-h structured clinical interview (Wittchen et al., 1997). The protocol was the same as described in our previous study (Hilti et al., 2013). A brief follow-up, approximately 1 year after study completion, revealed that two participants had proceeded to amputation in the meantime. Neurological, neuropsychological, and psychiatric examinations proved normal in all participants, including those with BID.

Table 2 lists the scores on the Zurich Xenomelia Scale and its three subscales (Aoyama et al., 2012). The subscore "amputation desire" is the mean score of 4 items enquiring the identity restoration as the primary motivation for the desire for amputation. The subscore "erotic attraction" is the mean score of 4 items asking for the erotic attraction towards amputated bodies. The subscore "pretending behavior" is the mean score of 4 items asking for the inclination to mimic an amputee (e.g., by using wheelchairs or crutches). The "total scale score" is the mean of all the 12 items and quantifies the strength of the desire for amputation. Each item has a Likert-type format, and answers can range from 1 to 6. Two of the 4 items of each subscale are formulated, such that 1 represents the least strong expression of the critical thought or behavior and 6 the strongest expression. For the other 2 items, this assignment is reversed.

Table 2. Characteristics of the participants with BID.

Participant	**Age (years)**	**Education (years)**	**Scanner (Place)**	**Mean scores on Zurich Xenomelia Scale (SD)**			
				Subscale 'amputation desire'	**Subscale 'erotic attraction'**	**Subscale 'pretending behavior'**	**Total scale score**
1	36	13	Milan	4.5 (2.4)	4.3 (2.4)	5.0 (2.0)	4.6 (2.1)
2*	36	13	Milan	5.3 (1.5)	3.3 (1.5)	3.0 (0.8)	3.8 (1.6)
3	48	18	Milan	6.0 (0.0)	3.5 (1.7)	4.0 (2.3)	4.5 (1.9)
4	34	18	Milan	5.3 (0.5)	2.8 (1.3)	3.3 (2.1)	3.8 (1.7)
5	37	18	Milan	6.0 (0.0)	6.0 (0.0)	4.8 (1.9)	5.6 (1.2)
6	41	13	Milan	6.0 (0.0)	4.3 (2.4)	5.5 (1.0)	5.3 (1.5)
7	39	18	Milan	5.8 (0.5)	4.5 (1.0)	5.0 (2.0)	5.1 (1.3)
8	64	13	Milan	6.0 (0.0)	5.5 (1.0)	4.5 (2.4)	5.3 (1.5)
9	41	18	Zurich	5.8 (0.5)	4.3 (2.4)	3.8 (2.6)	4.6 (1.7)
10*	46	18	Zurich	4.0 (1.8)	5.3 (1.5)	4.3 (1.5)	4.5 (0.2)
11	63	16	Zurich	5.5 (1.0)	2.5 (1.0)	4.0 (2.5)	4.0 (0.8)
12	57	18	Zurich	5.5 (1.0)	3.8 (1.5)	3.8 (2.2)	4.3 (0.6)
13	29	18	Zurich	5.0 (1.4)	6.0 (0.0)	4.3 (2.2)	5.1 (1.1)
14	28	18	Zurich	5.5 (1.0)	6.0 (0.0)	4.8 (2.5)	5.4 (1.3)
15	44	13	Zurich	5.8 (0.5)	3.3 (1.0)	4.0 (2.2)	4.3 (0.9)
16	67	18	Zurich	5.5 (0.6)	5.8 (0.5)	3.8 (2.6)	5.0 (1.2)

*Proceeded to amputation ~ 1 year after study completion

Magnetic resonance imaging data acquisition in Zurich

A 3.0 Tesla Philips Achieva whole-body scanner (Philips Medical Systems, Best, The Netherlands) was used to scan participants in Zurich. This scanner was equipped with a transmit-receive body coil and a commercial eight-element sensitivity encoding (SENSE) head coil array. For each participant, two high-resolution T1-weighted scans were acquired, applying a volumetric three-dimensional T1-weighted fast field echo sequence with a spatial resolution of 0.94 × 0.94 × 1.0 mm3 (acquisition matrix: 256 × 256 pixels, 160 slices) and lasted 468 s. Further imaging parameters were field of view, FOV = 240 × 240 mm2; echo time, TE = 3.7 ms; repetition time, TR = 8.06 ms; flip angle = 8°, and sensitivity encoding (SENSE) factor = 2.1. The two scans were co-registered and averaged, thus increasing the signal-to-noise ratio.

For each participant, we also collected resting-state functional MRI (rs-fMRI) spin-echo echo-planar imaging (EPI) scans. Participants were instructed to close their eyes and to let their minds wander. The rs-fMRI scans were obtained in the transversal plane with a spatial resolution of 2.5 × 2.5 × 4.0 mm3 (reconstructed 1.72 × 1.72 × 4.0 mm3). Imaging parameters were: TR = 4 s; TE = 35 ms; FOV = 220 × 220 mm2; slice thickness = 4 mm; number of slices = 40; SENSE factor = 1.8. The duration of the rs-fMRI sequence was 10 min, and 150 brain volumes were obtained for each participant

Magnetic resonance imaging data acquisition in Milan

For the sample acquired in Milan, we used a 1.5 T General Electric (GE) Signa HD-XT scanner. This scanner was equipped with an Echo Planar Imaging (EPI) gradient-echo sequence (flip angle = 90°; TE = 60 ms, repetition time (TR) = 3,000 ms, field of view (FOV) = 240 × 240 mm2 and matrix size = 64 × 64 pixels). For each participant, we collected a high-resolution T1-weighted image using a 3D-SPGR sequence (flip angle = 20°, TE= 2.92 ms, TR= 9.16 ms, acquisition matrix: 256 X 256 pixels; slice thickness=1mm, interslice gap = 0mm, and voxel size = 1 x 1 x 1 mm^3). The volumetric MRI scans consisted of 150 slices acquired on oblique sections parallel to the AC-PC line covering the entire brain volume. Rs-fMRI scans were acquired using the following parameters: Flip angle 90°, TE = 60 msec, TR = 3,000 msec, FOV = 280 × 210 mm2; matrix = 96 × 64 pixels). Each volume was composed of 35 contiguous oblique slices acquired along the AC-PC plane (thickness = 4 mm, gap = 0 mm). The duration of the rs-fMRI sequence was 10 min, and 200 brain volumes were obtained for each participant. The instruction given to participants scanned in Milan was the same as that used in Zurich.

Rs-fMRI Data preprocessing

Data preprocessing was performed, implementing the default preprocessing pipeline offered by the CONN connectivity Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) version 18b implemented in MATLAB (version 2016b, MathWorks, Natick, MA, USA). Rs-fMRI scans were preliminarily slice-time corrected. The realignment of all the rs-fMRI scans to the first one of the series was then performed. T1-weighed images underwent the unified segmentation algorithm (Ashburner & Friston, 2005). With this procedure, an estimation of the linear and nonlinear normalization of the T1-weighted MRI image was obtained. Estimated transformations were then applied to the functional images. Rs-fMRI scans were then spatially normalized to the Montreal Neurological Institute (MNI) template (voxel resampling to 2 x 2 x 2 mm^3). Consistent with the parameters used in our previous studies (Hänggi et al., 2017; Hilti et al., 2013) smoothing was performed using a Gaussian kernel of 6 mm full width at half maximum. Outliers scans in global signal and movement were identified with the Artifact Detection Tools (http://www.nitrc.org/projects/artifact_detect) and were defined as i) those whose scan-to-scan global signal differences was > 2 SD from the mean and ii) those whose compounded measure of movement parameters was > 2 mm scan-to-scan movement. After taking these steps, rs-fMRI scans were band-pass filtered within the range of 0.008 Hz to 0.09 Hz (i.e., the frequency range of physiological importance for measuring spontaneous neuronal activity (Biswal et al., 1995)). The variance related to translations and rotations using the six motion parameters (considered as first-level covariates) was regressed out, thus improving the signal-to-noise ratio. With the use of the CompCor strategy (Behzadi et al., 2007), the BOLD signal from the individual white matter and cerebrospinal fluid were also taken as confounds. No mean global signal regression was performed as the interpretation of the negative correlations observed after performing the mean global signal is still a matter of debate (Qing et al., 2015; Wong et al., 2012; Yeh et al., 2015)

Intrinsic functional connectivity of the cortical hubs

At the single-subject level, to map the intrinsic functional connectivity of the cortical hubs, we computed the intrinsic connectivity of individual voxel (ICC) applying the method described in Martuzzi et al. (2011) and implemented in the CONN toolbox. Based on network theory measures, ICC is a correlation-based connectivity approach that is sensitive to detect the presence and quantify the strength of the functional connections of a given voxel to the rest of the gray matter voxels in the brain. As such, ICC is a whole-brain measure that does not require a priori definition of any region of interest (ROIs). Another reason for preferring this index over other network degree-centrality indices (e.g., the degree-centrality index (Rubinov & Sporns, 2010; Sporns et al., 2007) is that ICC does not require to set an arbitrary threshold after correlating the temporal fluctuations of BOLD signals extracted from every brain voxel. ICC represents, therefore, a powerful and wholly automatized data-driven approach. Individual ICC maps were z-transformed with the Fisher's r-to-z transform function to obtain normally distributed data that allowed group analyses. To define the altered intrinsic functional connectivity in BID compared with the control groups, the z-transformed ICC maps of two groups were entered into a second-level random-effects analysis. Our design matrix consisted of 3 columns: i) BID individuals z-transformed ICC maps, ii) Controls z-transformed ICC maps, iii) the covariate “Scanner”. This covariate was introduced to account for the different scanners with which data have been collected. Note that the number of BID and control individuals tested in Zurich (8 vs. 8) and those tested in Milan (8 vs. 8) was the same. Decreased ICC in BID compared with controls, computed with the T-contrast BID < Controls [-1 1 0], indicated a breakdown of the intrinsic functional connectivity in the cortical hubs in the BID individuals. That is, the resulting cortical hubs were less connected to the rest of the brain in BID individuals compared with the controls. The opposite T-contrast, Controls > BID [1 -1 0] did not yield any significant results. The effects were extracted at $p < 0.001$ uncorrected at voxel-wise level and $p < 0.05$ at the cluster-level.

The BID Mask

The four regions of the AAL atlas corresponding to the lIFGOrb, the rPCL, the rSPL and the lITG were included in a brain mask that we called "BID mask". It was created with the Anatomy Toolbox implemented in SPM12 for the subsequent structure analyses, described below, aimed at detecting the cortical regions with an altered concentration of gray matter in BID compared with controls (see the Voxel-Based Morphometry analysis section). This mask also included three regions of the AAL3 atlas whose alteration was predicted from previous studies investigating morphological abnormalities in BID individuals compared with the controls. One was the AAL3 region labelled as "right insula" corresponding to the coordinates of the two clusters of the anterior insular cortex (upper cluster: $y = 32$ $x = 25$ $z = 9$, lower cluster: $x = 32$ $y = 20$ $z = -4$) found altered in BID (Hilti et al., 2013). The other AAL3 regions were the one labelled as “left precentral gyrus” and “left inferior frontal gyrus, opercular" corresponding to the cluster of ventral premotor cortex (PMv, y = -50 x = 5 z = 22) and the region labelled as "left superior frontal gyrus" corresponding to the cluster of dorsal premotor cortex (PMd, x= -20 y = -4 z = 58) (Blom et al., 2016).

Voxel-based Morphometry analysis

The Voxel-Based Morphometry approach was adopted to identify patterns of altered concentration of gray matter in BID individuals compared with controls. The regions lying in the BID mask were considered in these analyses. Data preprocessing and analyses were performed with MATLAB R2016b (Math Works, Natick, MA, USA), and Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK). To comply with a standardized procedure, we ran the classic preprocessing batch "preproc_vbm.m" provided by the SPM12 toolbox under the folder "batches." The preprocessing steps were the following: i) Segmentation of the images to identify white and gray matter; ii) Creation of DARTEL templates and estimation of the deformations that produced the best alignment of all the images, performing iterative registrations of all the images to their average; iii) Warping of the gray matter to the MNI space iii) Application of a Jacobian modulation to preserve an absolute regional amount of gray matter from the distortion introduced by the stereotactic normalization; iv) Normalisation of Jacobian scaled gray matter images, using the deformations that were previously estimated v) smoothing using a Kernel Gaussian Filter of 8 x 8 x 8 mm, vi) Averaging of smoothed images; v) Thresholding of the tissue average to get an explicit mask; vi) Normalization of the bias-corrected images to the MNI space; vii) Averaging of the normalized bias-corrected maps; viii) Checking of the average images and the explicit masks in the "Check Reg" provided by SPM 12; ix) Computation of the tissue volumes for each subject. The preprocessed subject-specific maps of gray matter were used to examine the anatomical differences between BID individuals and controls in the predicted key regions. We performed a two-sample t-test for each of the voxels lying within the BID mask. Regional values were corrected using the local correlation (ANCOVA) approach that allowed us to establish the group differences for each voxel that cannot be explained by the linear relationship between the amount of gray matter of that voxel and the total amount of gray matter for each participant. Such an approach, supposed to be more flexible than the global proportional scaling(Peelle et al., 2012), was preferred because participants acquired with different scans belonged to the same group. Consistent with the ICC maps and seed-based FC analyses, the design matrix comprised 3 columns: i) BID preprocessed gray matter maps, ii) Controls preprocessed gray matter maps, iii) the covariate "Scanner". Atrophies in BID compared with controls are reflected in the T-contrast BID < Controls [-1 1 0] while hypertrophies are reflected in the T-contrast BID > Controls [1 -1 0]. We used the most conservative thresholding method available in SPM ($p < 0.05$ FWE voxel-wise) coupled with a cluster extent threshold of $k > 25$ to further exclude spurious findings. Indeed, false-positive results do not cluster in space(Forman et al., 1995; Lieberman & Cunningham, 2009).

STUDY 2.
SOMATOPARAPHRENIA

Where in the brain is "the other's" hand? Mapping dysfunctional neural network in somatoparaphrenia

By **Gianluca Saetta**, Lars Michels, Peter Brugger

Under review

Author contributions: GS conceptualized the project and designed the study. GS wrote the manuscript. LM, PB reviewed and wrote sections of the manuscript. GS, LM collected the data. GS performed the clinical interview. PB supervised the clinical interview. GS, LM performed data analyses. LM supervised data analyses

ABSTRACT

Somatoparaphrenia (SP) refers to the delusional belief, typically observed in right brain-damaged patients, that the contralesional limbs belong to someone else. Here, we aimed to uncover the neural activity associated explicitly with this productive, i.e. confabulatory, component in a patient, S.P.P, with a large right-sided lesion of both cortical and subcortical gray and white matter. He claimed that his left paralyzed hand belonged to his mother. In a block-design functional magnetic resonance (fMRI) experiment, S.P.P. imagined that the mother would move her (i.e. his left) hand (condition "mother"). Subtraction of the activity elicited by control conditions (imagery of self-generated movement of either left or right hand) from that in the "mother" condition resulted in the focal activation of the pars opercularis of the right inferior frontal gyrus (rIFG). In a separate resting-state fMRI experiment with S.P.P. and 21 healthy controls, we examined the functional connectivity of the rIFG and the affected hand somatosensory network to the rest of the brain. We found a negative correlation between the activity in the rIFG and that of the Broca area and the temporo-parietal junction in the left hemisphere. Furthermore, the affected hand somatosensory network was disconnected from the left secondary somatosensory cortex. Our results link the productive component of SP to the activity of crucial hubs for integrating the multimodal signals of the affected hand. Furthermore, they provide the first direct evidence supporting the "left narrator model", proposed by Halligan et al. (1995), according to which the confabulations of SP are due to hemispheric disconnection

INTRODUCTION

We typically attribute the limbs that we own to ourselves. Crucially for individualization and social perception, we learn at an early stage of our development to differentiate between our own and others' limbs. However, acquired brain lesions, notably to the right cerebral hemisphere, can induce various types of self-other confusions (Brugger and Lenggenhager, 2014). One such condition, most often observed in the acute phase of a stroke or haemorrhage, is known as somatoparaphrenia (SP; Gerstmann, 1942; Vallar and Ronchi, 2009, for review). The striking and distinctive characteristic of SP is its *productive* component. That is, patients not only fail to recognize ownership over a (paralyzed) limb, but actively misattribute it to someone else. They often produce confabulatory accounts surrounding the circumstances under which the foreign body part had appeared in the first line. Claimed owners are examiners or caregivers (Gandola et al., 2012; Invernizzi et al., 2013), or relatives, whether living (Bottini et al., 2002; Pugnaghi et al., 2012) or deceased (Nightingale, 1982). SP thus presents as a delusional belief, frustratingly resistant to confrontation (Ramachandran, 2012). Yet, implicit knowledge about ownership is often suggested by the character of the claimed owner (a *deceased* hand, Juba, 1949; a *paralyzed* brother, Benedek and Angyal, 1939; a *handicapped* nephew or a *clumsy* kitten, Paulig et al., 2000), a sister, who is in fact in a vegetative state, Pugnaghi et al., 2012). Also the symbolism of a patient's poetic inspirations may give testimony to a spared insight into what is overtly denied on a verbal level (Pugnaghi et al., 2012). Other co-occurring beliefs typically affect motor awareness in that patients tend to overestimate their abilities to move the paretic limb, and, in many cases, they energetically engage themselves in the active denial of their motor deficit, i.e. anosognosia for hemiplegia (AHP, review in Orfei et al., 2007). Although associated in most cases, SP has been described in patients with spared insight into hemiplegia (Invernizzi et al., 2013; Bolognini et al., 2014, Sakamoto et al., 2019). The prerequisite for the clinical picture of SP to ensue is almost invariably the presence of three deficits affecting the limb being experienced as not belonging to the self, i.e. (i) loss of proprioception, (ii) impaired feeling of touch (hemianesthesia), and (iii) the inability to move (hemiplegia; Romano and Maravita, 2019). In addition, patients with SP most often present a high-level disorder in exploring the contralesional hemifield (unilateral spatial neglect) and body side (personal neglect; Romano and Maravita, 2019).

One etiological hypothesis makes a tight connection between unilateral spatial neglect and SP postulating that, due to the cerebral lesions of the right hemisphere visuo-spatial networks, patients with SP lack an accurate representation of the position of the affected limb in space. (Bisiach & Berti, 1987; Zingerle, 1913). That is, patients mentally and implicitly mislocate the limb, and even through direct visual inspection it is not possible to adjust the distorted spatial representation (Bisiach & Berti, 1987; Zingerle, 1913). Another model to explain the delusional ideation associated with AHP and SP is based on Geschwind's (1965a,b) influential views of interhemispheric disconnection. Specifically, Halligan et al., (1995) interpreted their patient's somatoparaphrenic delusions as the attempt of the "left hemisphere's narrator" (Gazzaniga, 2000) to make sense of the distorted sensorimotor information coming from a partially disconnected right hemisphere. The hypotheses and models provided so far (see Romano and Maravita, 2019, for a more comprehensive review) do not clearly distinguish between two substantially different conditions, AHP and SP, respectively. AHP involves delusional beliefs about own motor functions, SP is primarily a delusion of ownership. While an extensive literature addresses the neural mechanisms producing the delusions of AHP (see Pacella et al., 2019 for a recent account), the exploration of the productive component of SP has surprisingly not reached the attention it deserves. In particular, the idea of somatoparaphrenic delusions as reflecting a disconnection of the right parieto-temporal cortex from a left hemisphere linguistically competent monitoring system has, to the best of our knowledge, never been empirically tested.

Here, we present the case of a 76 year-old right-handed gentleman, S.P.P. (acronymic initials from ancient Greek for somatoparaphrenia, *Soma (*body*) - Para (*next to, in addition*) -Phrèn (*nerve)), who suffered an ischemic stroke leaving him with a large lesion of both cortical and subcortical gray matter (GM) and white matter (WM) of the right hemisphere. He was hemiplegic, but not anosognosic for his motor deficits and he showed signs of mild left-sided spatial, but no personal neglect. S.P.P. denied ownership for his left, paralyzed hand and claimed that it belonged to his mother, who had recently died in the very same hospital he was admitted to some days later.

We used a combination of active-task functional magnetic resonance imaging (fMRI) to map the brain activity distinctively linked to the content of S.P.P.'s delusion, and resting-state fMRI (rs-fMRI) to reconstruct the functional connectome of SP. Twenty-two days after the stroke, S.P.P. participated in a block-designed fMRI experiment; a classical motor imagery task which requires subjects to imagine performing open/close movements of a hand. We specifically tested motor imagery of the intact, right hand (MI R), the left, hemiplegic hand under volitional own control (MI L_{own}), and the left, hemiplegic hand *as moved by his mother* (MI L_{mother}). We identified the brain areas that are more activated by MI L_{mother} as contrasted to MI L_{own} and those more activated by MI L_{mother} as contrasted to MI R. We reasoned that the overlap of these two contrasts would allow for the localization of the areas specifically involved in the productive aspect of SP (SPC+), net of the underlying motor recruitment required by the task. We also looked at the neural responses triggered by MI R, and MI L_{own} separately, to ensure that S.P.P. was sufficiently committed with the task to recruit the typical fronto-parietal neural networks for MI. In a separate resting-state fMRI experiment with S.P.P. and 21 healthy controls matched for age and formal education, we tracked the alteration in S.P.P. of i) the functional connectivity (FC) in the right sensorimotor network (rSMN), given its involvement in bodily processing, and ii) the FC of the SPC+ area with the rest of the brain. We predicted SPC+ to be located in a multimodal integration area for bodily processing. In support of the left hemisphere narrator model, we predicted alterations in functional interhemispheric communication.

METHODS

Case Report

S.P.P. is a 76-year-old right-handed man with the minimum compulsory formal education (8 years). He was born in Italy and moved to Switzerland at the age of 20. He is divorced and has 4 children. He is living independently and autonomously. After an uneventful neurological and psychiatric history, he was admitted to the neurology clinic at the University Hospital of Zurich for a cerebrovascular ischemic insult. The computed tomography (CT) perfusion and CT angiography showed a demarked infarction of the right arteria cerebri media, a long-distance occlusion of the right internal carotid, suspected thrombus in the M1-Segment of the right arteria cerebri media, and an acute fronto-temporal subdural hematoma (see Figure 1).

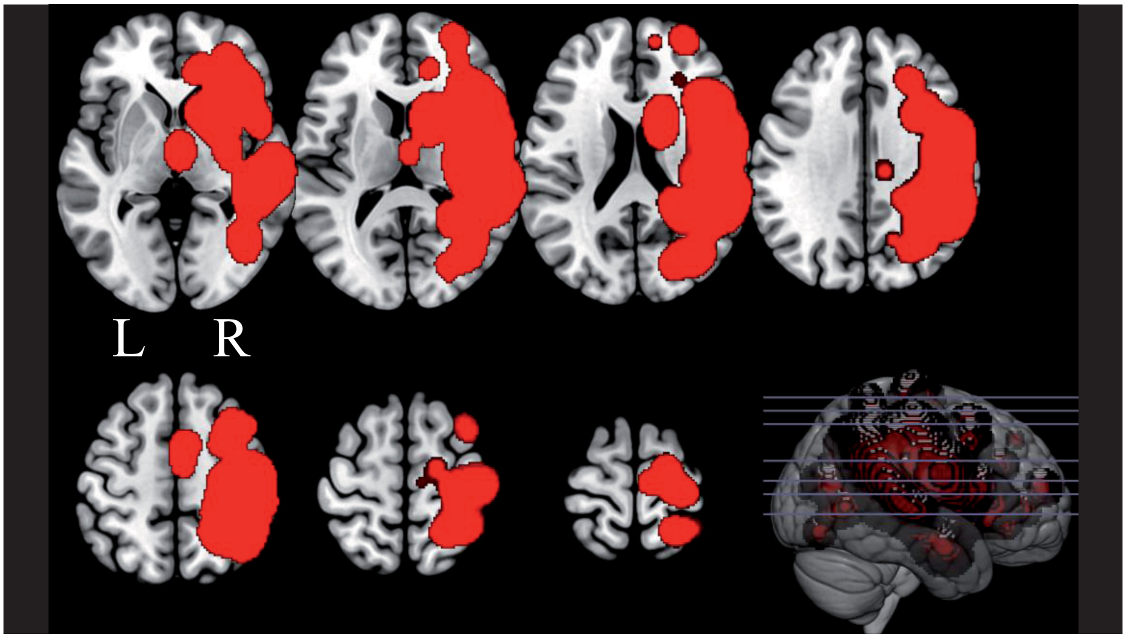

Figure 1. S.P.P.'s brain lesion mapping. Lesioned areas are displayed in red. Images shown in the neurological convention. L, left hemisphere. R, right hemisphere

The first routine neuropsychological examination, performed 4 days after the stroke, evinced the presence of left spatial neglect, severe dysarthria (i.e., a slurred speech due to bucco-facial muscles weakness), but no sensory aphasia as he could easily follow all verbal prompts. S.P.P. was completely hemiplegic, as his paralysis and hemianesthesia affected both upper and lower limbs. On the 22nd day after the stroke, left hemiplegia was still prominent, with the hemianaesthesia receded to a hypoesthesia with a preserved sense of pain. Gaze was slightly shifted to the left, but head position was always straight. Line bisection indicated the presence of a mild left-sided neglect (Schenkenberg et al., 1980); S.P.P. did not neglect, however, the left side of his body (see below). His dysarthria had become mild, there was no aphasia, but a marked psychomotor slowing. Personal neglect, AHP, and SP were formally tested on three consecutive days (22nd, 23rd, and 24th day after the stroke). Over the course of these 3 examinations, S.P.P. was constantly alert and well oriented in space, though with fluctuating perception of time. His mood was adequate; that is, he was neither depressed nor anosodiaphoric, but looked to the future full of hope.

Neuropsychological assessment of personal neglect

S.P.P. had no personal neglect as he could reach for the left hand with the intact right hand (score 0 on the Bisiach scale (Bisiach et al., 1986), whereby 0 indicates that the patient promptly reaches for the target; 1 = the target is reached with hesitation and search; 2 = the search is interrupted before the target is reached; 3 = no movement towards the target is performed.). This score was consistent across the three examinations to follow.

Neuropsychological assessment of AHP

AHP was assessed through use of the Bisiach 4-point scale for anosognosia (Bisiach et al., 1986). S.P.P. scored 0 (indicating that he reported the disorder spontaneously or after being asked a general question about his condition) in each of the three sessions. Moreover, 10 unimanual actions (separately for the left and the right hand) as well as 10 bimanual actions were employed to assess S.P.P.'s ability to evaluate his own motor performance. S.P.P. was asked: *"Are you able to perform this action? If you think you can perform it as usual, please say "yes", or if you're no longer able to perform it please say "no", or please say "partly" if you are no longer able to perform it as usual but still can perform it."* He was then asked to perform the movement and to verbally rate perceived movement quality on a continuous scale from 0 to 5 (0 = no movement execution, 5 = flawless movement execution). Unimanual actions were: snap the fingers, blow a kiss, comb, give a military salute, drink from a glass of water, shake a bunch of keys, make a scribble, blow the nose with a handkerchief, grab a ballpoint pen, brush the teeth, and wave to the examiner. Bimanual actions were: put on gloves, hold a tray, make up the face, play the triangle, open a bottle, take off the eyeglass with both hands, wash the hands, tie a knot, close both ears, and clap. S.P.P. answered "yes" to all the questions related to the right hand unilateral movements, correctly executed them and rated performance quality as 5 in each instance. He answered "no" to all the questions for the left unilateral and the bimanual actions (mean quality rating = 0.0).

Neuropsychological assessment of SP

SP was investigated through an interview that progressively tapped into the content of the delusion over the ownership of the hand. What follows are excerpts of the interview conducted on the 22nd day after the stroke.

Examiner E: Where is your left hand?

Patient S.P.P.: (after looking at the left hand, and then reaching for it with the right hand): this is my mum's hand. Here are her fingers.

E: (after positioning S.P.P.'s left hand in the mid-sagittal plane while S.P.P. kept the eye closed, and then asking to open the eye again once the left hand was in front of the face): Whose hand is this?

S.P.P.: This is my mum's hand.

E: Where is your mother?

S.P.P.: (pointing with the right index finger behind his left shoulder): she is here.

E: Is she behind you?

S.P.P.: yes, she is dead.

E: She is dead?

S.P.P.: Yes. [First] I didn't know. She died nine days ago.

Subsequently, S.P.P. was seated comfortably on a chair with his arms and hands stretched out on a desk/table, palms down. The examiner placed a mirror to the left of S.P.P.'s left hand.

E: (pointing to S.P.P.'s intact hand): Whose hand is this?

S.P.P.: this is mine.

E (pointing to S.P.P.'s left hand as reflected in the mirror): whose hand do you see in the mirror?

S.P.P.: this is mine.

E: Is it the left or the right hand?

S.P.P.: the left

E: can you move it?

S.P.P.: No, I can't (reaches for the left hand with the right hand)

E: can you move the right hand?

S.P.P. (moves the right hand)

The same interview was performed on the other two days. Results were consistent. The MRI, active-task and the resting-state fMRI examinations were performed on the 24^{th} day after the stroke.

MRI and fMRI and resting-state fMRI acquisition parameter

All MRI images were obtained using a 3.0 Tesla Philips. 3T Ingenia system (Philips. Medical Systems, Best, the Netherlands) using a 32-channel Philips head coil. 3D T1-weighted (T1w) structural images were acquired with a Turbo Field Echo sequence with the following parameters: repetition time (TR), 8.5ms; echo time (TE), 3.9ms; flip angle (FA), 8°; number of slices, 170; slice thickness, 1mm; field of view (FOV), 240 x 240 x 160mm^3; matrix, 240 x 240 and isotropic voxel 1 x 1 x 1 mm^3 and a scan time of 290 seconds. A rs-fMRI run (performed before the task fMRI) was acquired using an echo-planar-imaging sequence with the following parameters: TR, 2100ms; TE, 35ms; FA, 90°; number of slices, 30; FOV, 230 x 128 x 230mm^3; matrix, 64 x 63; voxel size, 3.6 x 3.6 x 4.0mm; and a scan time of 361 seconds. To minimize head motion, cushions were placed around the head. For the task fMRI scans (scanned in the order MI R, MI L_{own}, MI L_{mother}), the same scanning parameters were used but scanning time was only 201 seconds.

Voxel-based Lesion Mapping

The T1w scan, acquired 24 days after the stroke, was used to map the lesion. We implemented the robust automated voxel-based gaussian naïve Bayesian classification method described in (Griffis et al., 2016). The advantage over the classical manual lesion delineation is that this procedure less prone to subjective bias. This analysis was run with MATLAB (version 9.10), and SPM12 (Statistical Parametric Mapping, Wellcome Trust, UK), and the run scripts are included in the SPM extension “lesion_gnb” by J. Griffis (Griffis et al., 2016). A lesion mask in the Montreal neurological institute (MNI) space was obtained and was manually and carefully checked to exclude possible software artifacts. The locations of the GM lesion were identified with the Automated Anatomical Labeling map (AAL template, Tzourio-Mazoyer et al., 2002). WM damage was mapped with the Johns Hopkins University DTI- based white-matter atlas (JHU, Mori et al., 2008)). MRICRON software was used to calculate the number of voxels of the labelled region, the number of damaged voxels within the labelled region, the percentage of the lesioned tissue within the labelled region. This percentage is obtained by dividing the number of damage voxel by the number of the voxel of the labeled region. Figure 1 displays the damaged regions. Table 1 in the supplementary materials reports the descriptive statistics of the damaged gray matter AAL regions. Table 2 in the supplementary materials reports those of the damaged WM JHU regions.

Mapping mother's hand in the brain. A motor imagery fMRI experiment

Motor Imagery Training

Before being put in the scanner, S.P.P. underwent a motor imagery training. This was administered after each neuropsychological examination, i.e. on three sessions one day apart. The examiner first showed S.P.P. how to execute the real movements with the right hand with the forearm lying in a supinated position, keeping the eye closed and opening/closing the hand at a frequency of about 1Hz for 5 times. S.P.P. was then asked to execute the same motor task. After a few trials, S.P.P. was able to complete the task at the desired frequency. Afterward, S.P.P. was required to *imagine* performing the same movement keeping the eye closed and evoking the sensory and kinesthetic sensations he had experienced while previously performing it, avoiding overt motion. A strong emphasis was put on the use of a first-person perspective as opposed to a third-person perspective, i.e. S.P.P. was carefully instructed not to watch himself or others, including his mother, performing the movements. S.P.P. was then asked to imagine the same open-close movement but once with the left hand and once as if his mother would move her hand.

The second phase of each training session simulated the fMRI examination. S.P.P. was lying on the bed, and the examiner put a tablet in front of his face. S.P.P. was asked not to move his head throughout the session. On this tablet, alternating black and green full screens were presented. Black cued S.P.P. to rest, green invited him to imagine the opening/closing sequence of the hand. The onset of the black and green screens was random. Specifically, presentation of the black pictures varied between 8-10 seconds, and green images were presented in a random fashion between 15-20 seconds. Each block consisted of seven black and six green images. Both the training and the block-designed fMRI experiment consisted of three separate blocks where

S.P.P. imagined the movement with the right hand (MI R), with the mother's hand (MI L_{mother}), and with the left hand (MI L_{own}). Three separate runs corresponding to the three blocks were performed in the scanner. One examiner was physically next to S.P.P. in the scanner room throughout the whole experiment, to ensure that S.P.P. was not moving his head or his mouth, nor any limbs.

Data analysis

Data preprocessing and single-subject analysis was performed with Matlab (version 2016B) and SPM12. Preprocessing followed a classical procedure consisting in the realignment; normalization to the MNI template and interpolation of the data matrix to produce 2x2x2 mm voxels; spatial smoothing with an 8x8x8 mm Gaussian filter to improve the signal-to-noise ratio. After preprocessing, the canonical hemodynamic response function was used to characterize the Blood-oxygen-level-dependent (BOLD) signal associated with each MI task as opposed to its baseline condition. Artifacts, such as the physiological noise due to cardiac and respiratory cycles, were filtered out with the high-pass filtering (128 sec). The six motion parameters of each run were inserted to account for the variability introduced by translations and rotations of the head. We performed the following comparison: brain areas that are more activated by MI mother as contrasted to MI R (MI L_{mother} > MI R), and MI L_{mother} > MI L_{own}. We reasoned that the overlap of the results of these two comparisons would have allowed for the localization of the area(s) involved in the positive aspect of the SP, net of the underlying motor recruitment required by the task. The effects were extracted at $p < 0.001$ uncorrected at the voxel-wise level, and a cluster extend threshold of $k > 25$ was applied to exclude spurious findings, as the false-positive results do not cluster in space (Forman et al., 1995; Lieberman & Cunningham, 2009). We also looked at the neural responses triggered by MI R, and MI L_{own} separately to ensure that S.P.P. was engaged with the task of recruiting the typical neural networks for MI. The effects were extracted at $p < 0.005$ uncorrected at voxel-wise level and $k > 25$.

Resting-state functional connectivity

Healthy elderlies control group

The group of healthy elderly controls were 21 right-handed men within S.P.P.'s age range (mean 73 years, range 62 - 81). None of them showed a cognitive impairment (Mini Mental State Examination score ≥ 28 (out of 30)). The MRI for these controls was recorded prior to this study but used the same rs-fMRI parameters as described above. None had any history of major psychiatric or neurological disorders. The protocol was approved by the local ethics committee (BASEC: EK 22/2009), the informed consent was previously obtained by all the participants, and the experiment was carried out in accordance with the Declaration of Helsinki (1964).

Data Preprocessing

MATLAB (version 2016b, MathWorks, Natick, MA, USA) and CONN connectivity Toolbox version 18b (Whitfield-Gabrieli & Nieto-Castanon, 2012) were used for both preprocessing and further analyses. Data preprocessing followed the steps indicated by the default pipeline offered by CONN. Rs-fMRI functional scans were realigned to the first scan of the series and unwarped, centered to the anterior commissure, and slice-timing corrected. The artifact detection tools (ART http://www.nitrc.org/projects/artifact_detect) identified the outlier scans in the global signal and movements, classified as those > 2 SD from the mean of the scan-to-scan global signal differences, and those whose compounded measure of scan-to-scan movement was > 2 mm. Structural T1w scans were centered to the anterior commissure, submitted to the unified segmentation algorithm. The estimation of the linear and non-linear transformation was gathered. These parameters were applied to the realigned, slice-timing corrected, and trimmed rs-fMRI scans, which were normalized in the MNI space and resampled to 2 x 2 x 2 mm^3. A Gaussian kernel of 6 mm full width at half maximum was then used to perform smoothing. Preprocessed functional scans were band-pass filtered within the frequency 0.008 Hz to 0.09 Hz, i.e. the range commonly to sample the spontaneous neuronal activity not due to the cardiac and respiratory cycles (Biswal et al., 1995). To improve the signal-to-noise ratio, the estimated motion parameters, the BOLD signal from the individual white matter, and cerebrospinal fluid (CSF) masks were taken as confounds. Additionally, and exclusively for S.P.P., the variance in signal unrelated to brain activity and caused by the presence of the lesion was accounted by classifying the WM and GM voxels lying within S.P.P.'s lesion as CSF. Conforming to a widely-used procedure (Yourganov et al., 2018), the GM, WM and CSF signal from the lesion was regressed out. For all the participants, the global signal was not regressed out as the interpretation of the negative correlations is still debated (Qing et al., 2015; Wong et al., 2012; Yeh et al., 2015).

Seed regions of interest

To map the rSMN, we applied the well-established default procedure offered by CONN conforming to a seed-to-voxel whole-brain analysis with the seed corresponding to the affected hand sensorimotor network. To map the FC of SPC+, the significant cluster in the rIFG obtained from the comparison MI L_{mother} > MI R was used as a seed in a seed-to-voxel whole-brain analysis. The cluster yielded by this comparison was preferred over that of MI L_{mother} > MI L_{own}, as the former was more spatially extended and covered all voxels of the latter.

Seed-to-voxel analysis

At the single-subject level, the mean BOLD time course was extracted from the seed regions of interest and correlated with that of each voxel of the brain. Separate individuals' correlation maps were then generated for the FC of rSMN, and the FC of the SPC+. To allow second-level analyses, the correlation coefficients contained in each map were converted to normally distributed z-scores through Fisher's r-to-z transform function. These individual maps were inserted in two separate second-level analyses, one for the FC of the rSMN, and the other for the FC of the MBA. One-sided independent t-tests were performed. S.P.P. was considered as "patients group" and equal variances across groups were assumed. Indeed, performing a between-groups comparison with one group consisting of only one patient is equal to forming a normative sample and comparing the patient to it. Results were extracted at $p <$ 0.001 uncorrected at the voxel-wise level, with an FWE cluster-level correction ($p <$ 0.05). In case of a group differences, for each participant, we exported the strength of the FC values of each participant expressed by the Pearson's correlation coefficients. This was done to interpret the pattern of reduced FC changes that we found and are described below in terms of disconnection, anti-correlation, or reduced positive correlation between the BOLD time course of these two regions in S.P.P. compared to controls.

Voxel-based Morphometry analysis

The voxel-based morphometry analysis was performed to ensure that the average of the concentration of GM in the SPC+ was not significantly different between S.P.P. and controls. In MATLAB and SPM12, the standard preprocessing procedure offered by the "Computational Anatomy Toolbox 12" (Qing et al., 2015; Wong et al., 2012; Yeh et al., 2015) was applied. After preprocessing, the subject-specific GM maps were submitted to two one-sided independent t-tests. One examining the differences in the concentration of GM in all the brain voxels (whole-brain analysis) and the other considering the voxels laying within the ROI corresponding to the significant cluster in the rIFG obtained from the comparison MI L_{mother} > MI R. S.P.P. was considered as "patients group" and equal variances across groups (S.P.P. and controls) were assumed. Regional values were corrected using the global proportional scaling (Peelle et al., 2012). The effects were extracted at $p < 0.001$ uncorrected at the voxel-wise level, and a cluster extend threshold of $k > 25$ was applied.

RESULTS

Brain activity of the productive component of somatoparaphrenia

The comparison MI L_{mother} > MI R revealed an activation of the pars opercularis of the rIFG, MNI coordinates: x = 62, y = 20, y =18, p = 0.01 FWE voxel-wise corrected, see Table 1). Increased activity of the rIFG at the same location was registered while comparing MI L_{mother} > MI L. For this comparison, another focal activation was seen in the left postcentral gyrus (MNI coordinates: x = -56, y = -12, x = 34, $p < 0.001$, see Table 1). Results are displayed in Figure 2. Notably, both the whole-brain and the ROI-based voxel-based morphometry analyses showed that the concentration of GM within the rIFG was not significantly reduced in S.P.P. with respect to the controls.

The control analyses showed that in the MI R condition, S.P.P. was activating the typical fronto-parietal networks for MI. In particular, peaks of activation were located at the level of the left frontal operculum (significant cluster extending to the pars opercularis of the left inferior frontal gyrus), left supramarginal gyrus (significant cluster extending to the left parietal operculum and the left angular gyrus), left middle temporal gyrus, the right angular gyrus, and the precuneus bilaterally. Conversely, significant clusters for MI L_{own} were located in ipsilesional cortical (angular gyrus and posterior insula extending to the right parietal operculum) and subcortical (thalamus, putamen) regions as well as fronto-mesial structure (the medial segment of the left superior frontal gyrus extending to the right homologous area and the left supplementary motor area). Results are shown in Table 1 and displayed in Figure 3.

Table 1. Results of the motor imagery fMRI experiment

Brain regions	**MNI coordinates**							
	Left hemisphere				**Right hemisphere**			
	x	**y**	**z**	**Z-score**	**x**	**y**	**z**	**Z-score**
MI L_{mother} > MI R								
Inferior frontal gyrus, pars opercularis					62	20	18	5.02
MI L_{mother} > MI L								
Inferior frontal gyrus, pars opercularis					62	20	18	3.84
Postcentral Gyrus					-56	-12	34	4.16
Motor Imagery Right Hand								
Frontal Operculum	-42	18	10	3.24				
Middle Temporal Gyrus	-56	-40	2	3.24				
Supramarginal Gyrus	-58	-48	26	3.08				
Precuneus	0	-72	36	2.96				
Angular Gyrus					38	-50	16	3.39
Mother Imagery Left Hand								
Superior Frontal Gyrus	-2	54	16	3.05				
Superior Frontal Gyrus	-10	12	70	3.27				
Supplementary Motor Area	-2	54	16	3.01				
Angular Gyrus					46	-60	42	2.99
Posterior Insula					30	-20	16	2.99
Thalamus					6	-6	-4	3.46
Putamen					26	-2	16	3.32

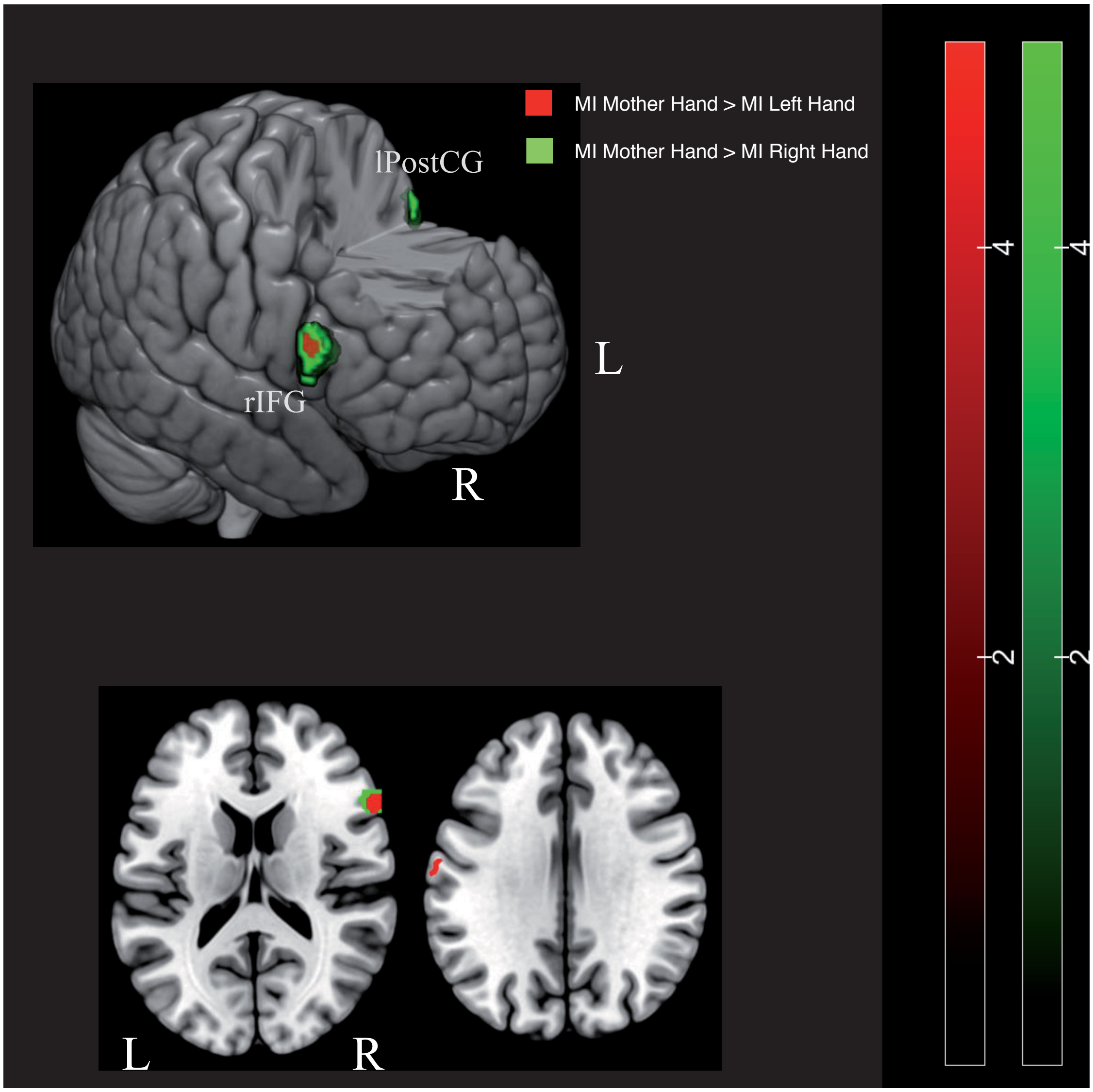

Figure 2. Results of the motor imagery fMRI experiment. Brain areas more hyperactivated during the imagery of mother rather than oneself moving the hand movements are displayed in red. More hyperactivated during the imagery of the mother's than the right hand movements are displayed in green. L, left hemisphere. R, right hemisphere; rIFG, right inferior frontal gyrus, pars opercularis; lPostCG, left post-central gyrus. Colorimetric bars express z-scores

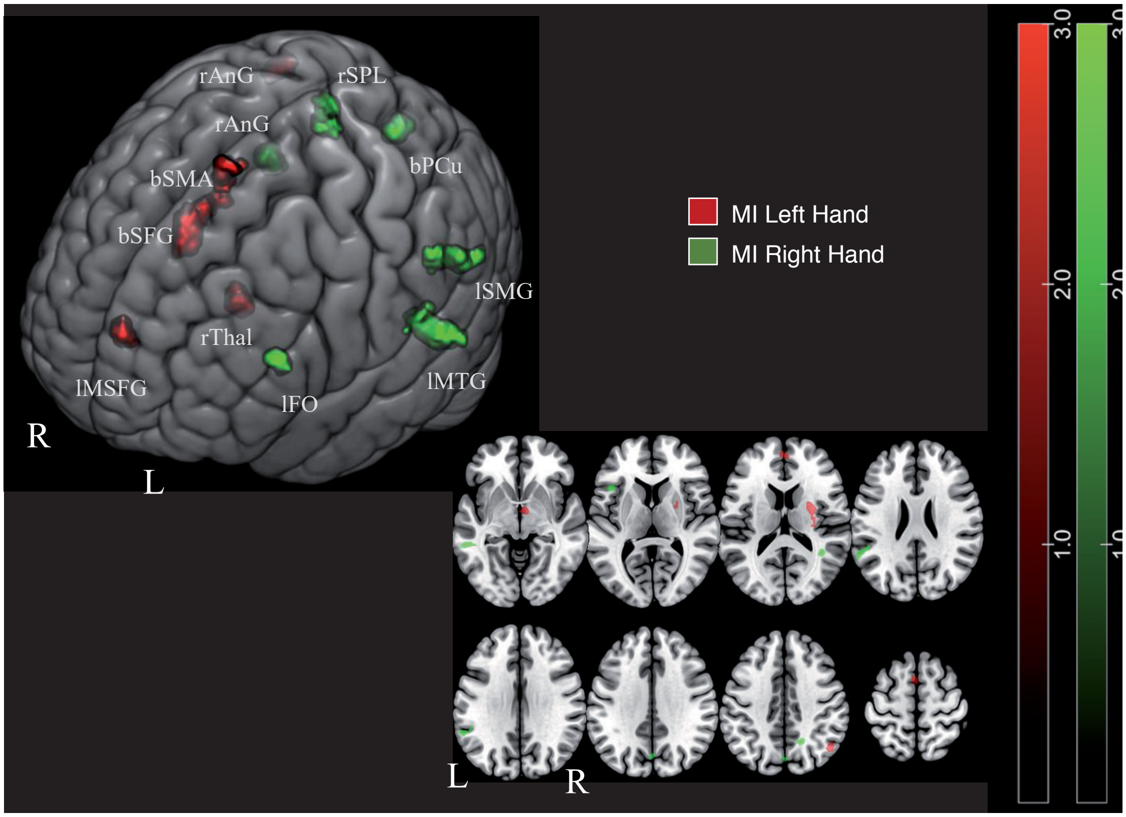

Figure 3. Results of the motor imagery fMRI experiment. Brain areas activated during the imagery of the left hand movements are displayed in blue. Brain areas activated during the imagery of the right hand movements are displayed in violet. L, left hemisphere. R, right hemisphere; lMSFG, left superior frontal gyrus, medial segment; lFO, left frontal operculum; bSFG: bilateral superior frontal gyrus; bSMA: bilateral supplementary motor area; rAnG, right angular gyrus; rSPL, right superior parietal lobule; lMTG, left middle temporal gyrus; bPCu, bilateral precuneus; lSMG, left supramarginal gyrus, rThal, right thalamus. Colorimetric bars express z-scores

The sensorimotor and the productive component networks of somatoparaphrenia

With reference to the rSMN, in S.P.P., the right postcentral gyrus, including the left hand area, showed a focally reduced FC to the left secondary somatosensory cortex (MNI coordinates: x = -56, y = -12, x = 34). In particular, while in controls these two regions were positively connected (group mean Pearson's correlation coefficient, r = 0.72, SD = 0.15), in S.P.P. they were disconnected (Pearson's correlation coefficient, r = -0.12, p < 0.001). In S.P.P., we also found a reduced FC of the SPC+ with one cluster in the left frontal lobe (including the frontal pole, the middle frontal gyri, and the pars triangularis of the inferior frontal gyrus; peak coordinates: x = - 46, y = 32, z = 22), and one cluster in left temporo-parietal junction (including the supramarginal gyrus, middle and superior temporal gyri, the parietal operculum, the angular gyrus, and the planum temporale; peak coordinates: x = -66, y = -50, z = 8). However, in S.P.P. we found two key patterns of anti-correlation; i) the more active the MBA, the less active the cluster in left frontal lobe (Pearson's correlation coefficient, r = -0.61), ii) the more active the MBA, the less active the left temporo-parietal junction (Pearson's correlation coefficient, r = -0.47). Results are shown in Figure 4.

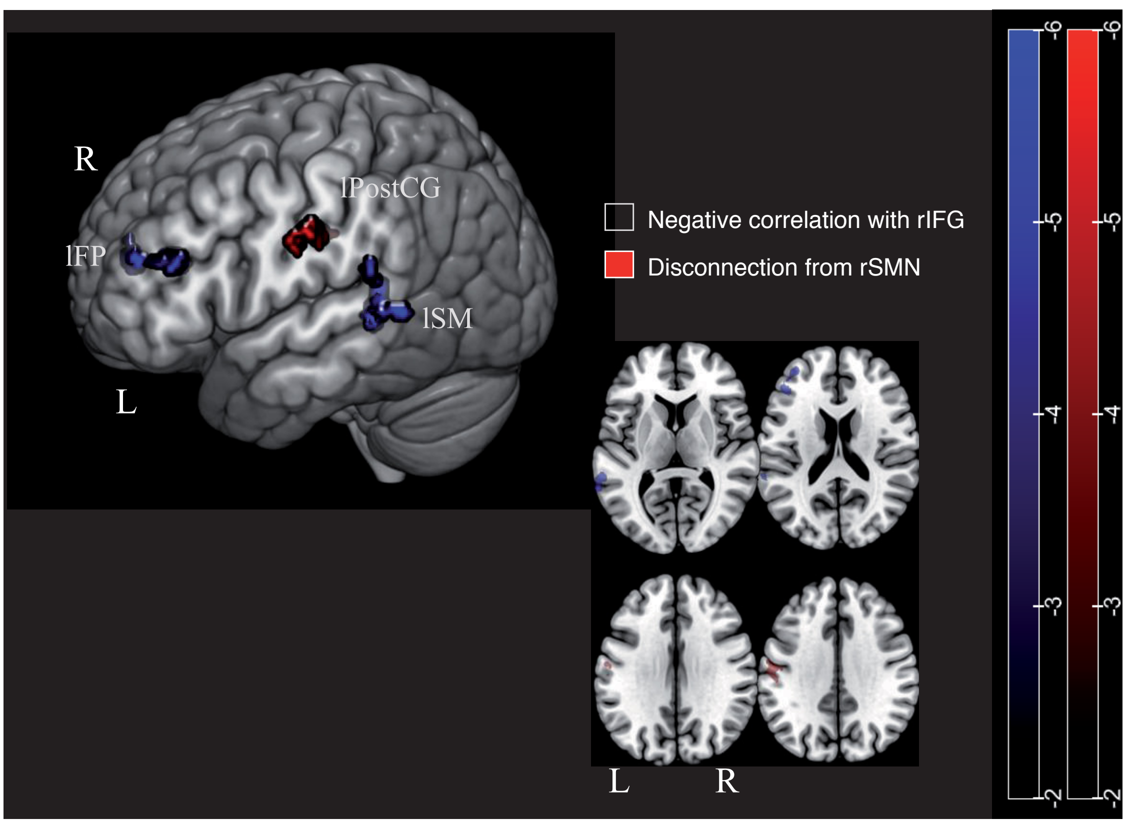

Figure 4. Resting-state fMRI experiment results. Brain areas anticorrelated to the pars opercularis of the right inferior frontal gyrus (rIFG) in S.P.P. compared with the healthy controls are displayed in blue. The brain area disconnected from the right sensorimotor

network (rSMN) in S.P.P. compared with the healthy controls is displayed in yellow. L, left hemisphere. R, right hemisphere. lFP, left frontal pole; lPostCG, left postcentral gyrus; lSM, left supramarginal gyrus.

DISCUSSION

Very few previous studies aimed at exploring the neural correlates of SP (review in Romano & Maravita, 2019). These studies looked at size, location and distribution of lesioned brain tissues in the affected individuals. The lesion mapping methods used have helped uncover the damage necessary for SP to occur. They do not, however, allow for the identification of the neural networks scaffolding the construction and maintenance of the productive component of the somatoparaphrenic delusion. The present work implemented functional imaging to overcome this limitation. Our findings shed new light on two crucial questions: (1) can delusional disownership be, at least to some extent, ascribed to a circumscribed alteration of the multisensory integration areas of the brain? 2) can functional neuroimaging provide evidence for a "left hemisphere narrator" model of SP, which predicts a breakdown in interhemispheric communication?

Somatoparaphrenia and multisensory integration in the brain

In response to the first question, our findings link the productive component of SP to the functional activity of the rIFG seen by the fMRI contrast MI L_{mother} > MI R and MI L_{mother} > MI L. The activity of the rIFG is thought to mediate the integration of the contralateral limbs' sensory input (i.e., spatial location, visual, tactile, vestibular, and re-afferent motor signals) departing from the primary somatosensory and motor areas. A proof of concept is the involvement of this area in the rubber hand illusion, whereby the simultaneous stroking of a real and a rubber hand, while the former is hidden and the latter is visible, creates the illusion of ownership over the latter (Ehrsson et al., 2004, 2005a; Tsakiris et al., 2007a). What emerges from such multisensory integration is the anchoring of the limbs to the body schema, i.e. the implicit and continuously updated representation of the location of single body parts in space. Multisensory integration is thus key for establishing a coherent bodily self and a sense of ownership (Blanke, 2012 for an overview). Lesions of the primary somatosensory and motor areas in the right hemisphere, like those observed in S.P.P., are likely to generate degraded or absent sensory input from the left hand. As a consequence, the enhanced activity of the rIFG might mirror the unsuccessful attempts in binding the distorted sensory information into a coherent unity of body and self. As previously suggested, such deficient multisensory integration may account for the spatial mislocation of the limb and the absence of the regular feeling of ownership (Romano & Maravita, 2019). In line with this perspective, Gandola et al., (2012) compared two groups of patients, one group with SP, the other without. The two groups were matched for the presence of neglect, hemiplegia and AHP. The authors reasoned that all between-group differences could be ascribed to the somatoparaphrenic delusion. They found a distinctive involvement in the SP group of the rIFG and the affected hand sensorimotor area.

Also compatible with this view, accumulating evidence in SP patients suggests that a transient reinstatement of limb ownership may occur when the multimodal integration of the limb can rely on spared sensorimotor input processed by intact brain areas. For instance, Bolognini et al., (2014) simultaneously stroked the disowned hand affected by hemianesthesia and the intact one, while only the disowned hand was visible. In this case, the alignment of the visual information from the disowned hand with an "alternative" and flawless source of tactile information "borrowed" from the intact hand would abolish the somatoparaphrenic delusion.

Another treatment of SP relies on a vestibular rather than tactile information source. Caloric vestibular stimulation consists of the irrigation of the left ear with cold water, which leads to a convection in the horizontal canal, a sensation of rotation, and reflexive eye movements (nystagmus). On a neural level, this stimulation triggers the activation of the right hemisphere "vestibular cortex" which includes, among other neocortical and insular regions, notably the rIFG (Lopez & Blanke, 2014). Such enhanced brain activity is thought to contrast the global functional depression of the right brain functional networks for body-space processing and may act against limb mislocalization. In any case, as long as the nystagmoid response to caloric stimulation holds up, left-sided neglect (Silberpfennig, 1941), anosognosia (Cappa et al., 1987), and, importantly, also SP (Bisiach et al., 1991) are all transiently abolished. Yet another method for the temporary reinstatement of limb ownership through multisensory integration of the spared sensory input consists of letting the patients see the reflection of the disowned hand through a mirror. In this way, S.P.P. and other previously described patients (Fotopoulou et al., 2011; P. M. Jenkinson et al., 2013) correctly attributed the hand to themselves. The mirror view provides visual information of the hand from a different perspective, i.e. from the "outside", inducing a translocation from an egocentric to an allocentric viewpoint. The multisensory integration in the natural view in the egocentric coordinates, from the "inside", activates sensorimotor fronto-parietal areas. However, the integration in the allocentric viewpoint relies to a larger extent on visual information in the occipital areas, which are typically not lesioned in SP patients (Fotopoulou et al., 2011). Nevertheless, the reinstatement of limb ownership lasts only as long as the patient refrains from switching back to looking at the limb from a natural perspective.

Taken together, the results of the previous and own studies clearly show that limb ownership depends on the multisensory integration, and that, in absence of input from a given sensory source, multisensory integration can still efficiently rely on different sources. The activation of the rIFG represents the neural substrate of such integration.

Somatoparaphrenia and inter-hemispheric communication

In reference to the second question to be addressed, previous studies suggested that the deficit of multisensory integration and limb disownership may be explained by the breakdown of the connectivity of the primary somatosensory areas rather than their lesions (Romano & Maravita, 2019; Saetta et al., 2020). In the words of Devinsky (2009, p. 80), "Delusions result from right hemisphere lesions. But it is the left hemisphere that is deluded". A proof of concept is the observation that the most abundant damages in SP are located at the level of the WM connecting i) the primary motor to the lower motor neurons in the spinal cord (corona radiata and the internal capsule (Gandola et al., 2012; Romano et al., 2015); ii) temporo-parietal areas to the frontal lobe (superior longitudinal fasciculus and superior fronto-occipital fasciculus), iii) the hippocampus, the thalamus (Gandola et al., 2012; Romano et al., 2015) and the basal ganglia (Moro et al., 2016; Romano et al., 2015) to fronto-temporo-parietal areas. The present findings complement previous ones by offering the first direct evidence for a *functional* disconnection in SP between the affected hand sensorimotor network from the left secondary somatosensory cortex. We recently described a similar disconnection effect, albeit targeting the *primary* sensorimotor cortex. In rational individuals with no major neurological or psychiatric disorders, but the desire for amputation of a healthy limb (Body Integrity Dysphoria, BID), a feeling of nonbelonging for that limb was tied to a lack of FC of its primary sensorimotor area (Saetta et al., 2020). The least common denominator between BID and SP is limb disownership (Ramachandran & McGeoch, 2007, but see Lenggenhager et al., 2014). However, apart from the fact that BID and SP are, respectively, developmental and acquired conditions, BID individuals are not delusional; they recognize the limb they want to remove as an undesirable extension of their "true" body, which lacks the limb. Importantly, they never misattribute the unwanted limb to someone else. Therefore, In BID and SP, the reduced FC of the limb sensorimotor area might reflect the *deficit* of a lack of ownership. However, the involvement of different neural networks may substantiate the *productive* component of SP. In the present work, we found that the less active the rIFG, the more active the fronto-parietal mirror network in the left hemisphere (including Broca area and the left parieto-temporal junction), the network that it consistently associated with the capacity of mapping actions, sensations, and emotions between the self and others in a social context (review in Gallese, 2006). In other terms, we found evidence for a disconnection between a failed multisensory integration in the right hemisphere and the route to verbal access in the left hemisphere, i.e. those instances dubbed "narrator" or "interpreter" originally in split-brain studies (Gazzaniga, 2000) and later in connection with SP (Halligan et al., 1995). In the absence of coherent right-hemisphere information, the left narrator may verbally confabulate. This confabulation is hinged on the loss of boundaries between the self and the others. Here we propose specific coordinates for this narrator, which overlaps with the left fronto-parietal mirror network. This proposal may help shape future task-based methodologies in the characterization of individual cases of SP. While there are methods to quantify deficits in body ownership (e.g., Chancel & Ehrsson, 2020), no adequate procedures have yet been described with respect to the productive components of SP. This is because of a lack of conceptual background. Our results suggest that measures of interhemispheric transfer could be used as a proxy to reflect a patient's inclination to attribute own body parts to somebody else.

Our study comes with several limitations. First, one may argue that we cannot guarantee that S.P.P. was really imagining moving his hand during the fMRI task. However, the activation of the typical fronto-parietal network for MI and the areas for body representation in the right hemisphere (superior parietal lobule and angular gyrus) during MI of the intact hand suggests that he did. Furthermore, the generalization of the present findings requires caution as they originate from a single-case investigation. Future studies should go beyond a n=1-design and recruit a group of patients with SP and one without, as exemplified in Gandola et al. (2012). Nevertheless, the strength of the present single-case report is that S.P.P. presents SP *without* AHP, ruling out possible contamination of the ownership delusion with that concerning the functionality of the paralyzed limb. A particular strength of the present findings is that we found a focal activation of the rIFG across different contrasted conditions with the results surviving multiple correction comparisons for fMRI data (FWE-correction). In view of a potential contribution of neuroimaging to the differentiation between insight and delusion, we have thus overcome the pessimistic statement that "it requires just as much oxygen to think an irrational thought than to think a rational one" (Kety, 1960, p. 1865-66). We have substantiated the proposal that, beyond differences in local oxygen consumption, the *functional connectivity* between widely separated brain regions may decide upon rational and irrational judgment.

We are well aware that the present data do not solve the riddles of SP once and forever. We assume that the phenomenological characteristics of an individual patient's somatoparaphrenic delusion may be as important as the knowledge about the neural circuitry involved in their production. To capture these characteristics requires paying "very close attention to exactly what the patient says" (Halligan et al., 1995, p. 181). this is why we would like to conclude with a note concerning the patient's identification of the paralyzed hand's owner as his mother. Apart from the fact that the patient's mother had indeed stayed in the very hospital the patient was admitted only days later (see Bisiach et al., 1991, p. 1030, for a very similar constellation of events), she passed away shortly before his infarction. In contrast to anxious, desperate or suspicious patients, who often identify "the other's" hand as that of a malignant or threatening being, our patient was mourning about a very beloved person, whose presence may have been consoling and contributing to his calm and often cheerful mood. It is our hope that future neuropsychoanalysis (see, e.g. Besharati & Fotopolou, in press) will succeed in unifying the neurological and psychological aspects of the puzzling accounts of somatoparaphrenic delusions.

SUPPLEMENTARY MATERIALS

Table 1 supplementary materials. Descriptive statistics of the damaged gray matter AAL regions.

Brain Region Region (AAL label)	*Total number of voxels*	*Number of lesioned voxels*	*Percentage of lesioned tissue*
Precentral_R 2002	27058	23504	0.869
Frontal_Sup_R 2102	32089	6681	0.208
Frontal_Sup_Orb_R 2112	7859	88	0.011
Frontal_Mid_R 2202	40374	17654	0.437
Frontal_Mid_Orb_R 2212	8057	368	0.046
Frontal_Inf_Oper_R 2302	11174	9077	0.812
Frontal_Inf_Tri_R 2312	17132	9138	0.533
Frontal_Inf_Orb_R 2322	13747	4288	0.312
Rolandic_Oper_R 2332	10733	10047	0.936
Supp_Motor_Area_L 2401	17282	1091	0.063
Supp_Motor_Area_R 2402	18885	5212	0.276
Olfactory_R 2502	2286	321	0.14
Frontal_Sup_Medial_R 2602	16979	1218	0.072
Frontal_Med_Orb_R 2612	6870	273	0.04
Rectus_R 2702	5930	125	0.021
Insula_R 3002	14128	11680	0.827
Cingulum_Ant_R 4002	10442	1801	0.172
Cingulum_Mid_L 4011	15512	1113	0.072
Cingulum_Mid_R 4012	17442	5788	0.332
Hippocampus_R 4102	7606	3664	0.482
ParaHippocampal_R 4112	9028	1491	0.165

Amygdala_R 4202	1965	1909	0.972
Calcarine_R 5002	14885	2428	0.163
Cuneus_R 5012	11323	1379	0.122
Lingual_R 5022	18450	262	0.014
Occipital_Sup_R 5102	11149	3993	0.358
Occipital_Mid_R 5202	16512	8005	0.485
Occipital_Inf_R 5302	7929	2699	0.34
Fusiform_R 5402	20227	2669	0.132
Postcentral_R 6002	30652	23590	0.77
Parietal_Sup_R 6102	17554	7739	0.441
Parietal_Inf_R 6202	10763	10512	0.977
SupraMarginal_R 6212	15770	14467	0.917
Angular_R 6222	14009	12237	0.874
Precuneus_R 6302	26083	1401	0.054
Paracentral_Lobule_R 6402	6693	798	0.119
Caudate_R 7002	7941	6647	0.837
Putamen_R 7012	8510	8492	0.998
Pallidum_R 7022	2188	2188	1
Thalamus_L 7101	8700	889	0.102
Thalamus_R 7102	8399	2518	0.3
Heschl_R 8102	1936	1899	0.981
Temporal_Sup_R 8112	25258	21139	0.837
Temporal_Pole_Sup_R 8122	10654	1911	0.179
Temporal_Mid_R 8202	35484	20104	0.567
Temporal_Pole_Mid_R 8212	9470	1088	0.115
Temporal_Inf_R 8302	28468	3355	0.118
Cerebelum_Crus1_R 9002	21017	86	0.004
Cerebelum_6_R 9042	14362	30	0.002

Supplementary Table 2. Descriptive statistics of the damaged white matter JHU regions.

Brain Region Region (AAL label)	***Total number of voxels***	***Number of lesioned voxels***	***Percentage of lesioned tissue***
Genu_of_corpus_callosum	8851	1169	0.132
Body_of_corpus_callosum	13711	1459	0.106
Splenium_of_corpus_callosum	12729	1585	0.125
Fornix_(column_and_body_of_fornix)	659	166	0.252
Cerebral_peduncle_R	2278	65	0.029
Anterior_Rimb_of_internal_capsule_R	3018	2967	0.983
Posterior_Rimb_of_internal_capsule_R	3752	1306	0.348
Retrolenticular_part_of_internal_capsule_R	2469	1584	0.642
Anterior_corona_radiata_R	6852	4181	0.61
Superior_corona_radiata_R	7508	1854	0.247
Posterior_corona_radiata_R	3714	2489	0.67
Posterior_thalamic_radiation_R	3978	3213	0.808
Sagittal_stratum_R	2231	982	0.44
External_capsule_R	5587	5527	0.989
Cingulum_(cingulate_gyrus)_R	2751	451	0.164
Fornix_(cres)_/_Stria_terminalis)_R	1125	331	0.294
Superior_Rongitudinal_fasciculus_R	6605	5517	0.835
Superior_fronto-occipital_fasciculus_R	507	491	0.968
Uncinate_fasciculus_R	376	376	1
Tapetum_R	600	589	0.982

STUDY 3. ASOMATOGNOSIA

Asomatognosia: structured interview and assessment of visuo-motor imagery

By **Gianluca Saetta**, Olivia Zindel-Geisseler, Franziska Stauffacher, Carlo Serra, Gilles Vannuscorps, Peter Brugger

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Author contributions: GS wrote the manuscript. PB conceptualized the project. GS, OZ, FS, CS collected the data. GS performed data analyses. OZ, FS performed the clinical interview. PB supervised clinical interview. GV and PB reviewed the manuscript.

ABSTRACT

Asomatognosia designates the experience that one's body has faded from awareness. It is typically a somaesthetic experience, which may spread to the visual modality. Frequently associated symptoms are the loss of ownership or agency over a limb. Here we elaborated on the rigorous nosographic classification of asomatognosia and developed a structured interview to capture both its core symptoms and associated signs of bodily estrangement. We additionally report the case of a pure left-sided hemiasomatognosia occurring after surgical removal of a meningioma in the right atrium. Notably, despite the wide lesions of the right angular gyrus and of the temporo-parietal junction, the patient did not present visuo-spatial deficits or bodily awareness disorders other than hemiasomatognosia. The patient and ten matched controls' motor imagery was formally assessed with a limb laterality task where they had to decide whether hands and feet presented under different angles of rotation depicted a left or a right limb. Bayesian statistics showed that patient's reaction times were significantly impaired exclusively for the left foot, and especially for mental rotations requiring somatomotor rather than visual limb representations. This was in accordance with a more enduring left-sided hemiasomatognosia for the lower limbs in the somesthetic modality. Our findings shed new light on motor imagery in asomatognosia and encourage the future use of the structured interview introduced here, and the limb laterality task to capture phenomenological elements of a case by chronometric means. This allows a more standardized reporting of phenomenological detail and improves communication across different clinical facilities.

INTRODUCTION

Asomatognosia is defined as the impression that one's own body has ceased to exist (Critchley, 1953). Most often, only one half of the body (usually the left) is affected ("hemiasomatognosia"), hence "the characteristic feature is a subjective sensation as if there existed nothing to the left of the midline of the body" (Critchley, 1953). This sensation is most typically a bodily feeling, i.e. the loss is somesthetic ("pure asomatognosia"), but it may spread to the visual modality. Thus, a patient of Carp's felt the right half of her body absent, but could convince herself that this somesthetic impression was in fact illusory by looking at the missing side and seeing it (Carp, 1952). Conversely, a patient with a right thalamic tumor felt his sensation of an absent left hemibody confirmed by looking at the void body space and not seeing his left side (Stockert, 1934). Cases in which the own body or parts of it have faded from vision, but can still be felt, are also described, but should explicitly be referred to as *visual* asomatognosia or asomatoscopy (Magri & Mocchetti, 1967, Arzy et al., 2006). Historically, the notion of asomatognosia as a "feeling of 'nothingness' (Critchley, 1953) has long remained undisputed. Apart from its scholarly treatment in Critchley's seminal volume on the parietal lobes, the phenomenon was discussed at length in the French and German literatures, and defined in accordance with the English language definition, as "sentiment d'absence d'une partie du corps" (Hécaen & de Ajuriaguerra, 1952) or as the (illusory) experience of amputation ("sentiment d' amputation", Cambier et al., 1984); "Amputationserlebnis", (Menninger-Lerchenthal, 1935). Mikorey (Mikorey, 1952) borrowed a term from zoology, to emphasize possible evolutionary-biological roots of asomatognosia ("psychologische Autotomie", psychological autotomy). Conceptually, in the tradition of European neurology, asomatognosia was thus uniformly viewed as a disorder of body schema, more specifically as a transient disruption of such a postural model of the body as proposed by (Head & Holmes, 1911) and previously described as "aschematia" by Bonnier

(L'Aschématie, 1905). In their historical review of the phenomenon, (G. Vallar & Papagno, 2003); see also (Dieguez & Annoni, 2013; Blanke et al., 2008) made it clear that pure asomatognosia is often seen in company of related disorders of a central representation of the body or, frequently, its left side. Already (Critchley, 1953) had listed different forms of unilateral neglect, anosognosia, anosodiaphoria, confabulatory denial of hemiparesis (somatoparaphrenia) and forms of sensations of "deadness" of parts of the body. In their recent, authoritative definition paper on asomatognosia (P. Jenkinson et al., 2018), appreciate the felt absence as the defining feature of the phenomenon, but also note the frequent association of asomatognosia with symptoms of non-recognition or misrecognition of own body parts. This association may have confused some authors in the past, as they mixed up associated symptoms and asomatognosia as originally defined. (Feinberg, 1997) for instance, introduced the "syndrome of asomatognosia" as "denial of ownership of the arm" (p. 130), thereby mistaking asomatognosia for somatoparaphrenia. Such blurring of related, yet distinct clinical manifestations of cerebral damage can induce confusion, especially when claims to neuroanatomical correlates are made. Thus, the purported distinction between neural contributions to asomatognosia on the one hand and somatoparaphrenia on the other (Feinberg et al., 2010) turns out to be non-informative and even misleading once asomatognosia is newly defined as "unawareness of ownership of one's arm" (p. 276). It is against this background that we here propose a structured interview for the assessment of asomatognosia and the description of associated symptoms (Appendix). We also describe a patient with pure hemiasomatognosia after extirpation of an intraventricular meningioma in the right atrium. We provide a detailed description of the characteristics of the experience. We also report the results of a visuo-motor imagery task (mental rotation of hands and feet) administered to the patient. We discuss the observed reaction time pattern with reference to the clinical symptomatology.

METHODS

Case Report

Patient ASG (acronymic initials for *A-S*omato-*G*nosia) is a 53-year-old right-handed woman with a master's degree in business management. She is divorced and has two adult children. After an uneventful neurological and psychiatric history, somatic complaints like headaches, vertigo and gait disturbances as well as cognitive symptoms such as forgetfulness and inability to concentrate led to the discovery of an intraventricular meningioma in the right atrium (Figure 1). Its dimension and considerable lateral extension made surgical removal by an interhemispheric route appear unfavorable and the meningioma was microsurgically removed via a transangular gyrus trajectory after right-sided temporo-parietal craniotomy.

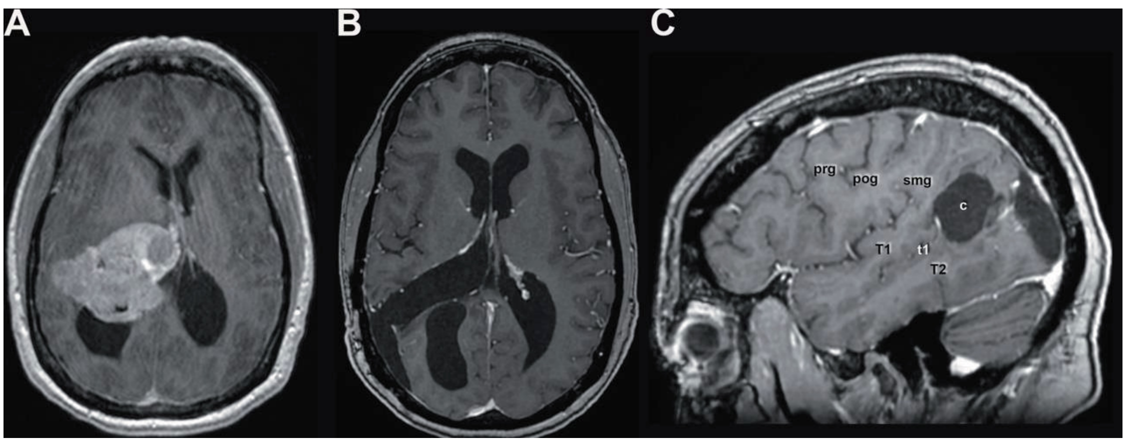

Figure 1. Pre- (A) and postoperative axial (B) and sagittal (C) MR scan with gadolinium showing the preoperative extent of the meningioma, filling the atrium and displacing anteriorly the thalamus and medially the third ventricle and velum interpositum thereby inducing a subocclusive hydrocephalus. Given the considerable lateral extent of the lesion, a lateral transcortical transangular approach was chosen rather than an interhemispheric transprecuneal approach which would be usually indicated for lesions in the atrium. The lesion was completely removed as illustrated in (B). (C) shows location and extent of the corticectomy in the angular gyrus. Legend: c, corticectomy; pog, postcentral gyrus; prg, precentral gyrus; smg, supramarginal gyrus, T1, superior temporal gyrus; t1, superior temporal sulcus; T2, middle temporal gyrus. Scans are shown according to radiological convention (right hemisphere on left side of image).

Two or 3 days after surgery, ASG noticed a sensory deficit in the left hand and foot, which alternated with the feeling of spasticity in these body parts. These sensations were waxing and waning, occurred approx. 3 times a day and typically lasted for some minutes. A neurological examination showed a slight spastic increase in tone in the left upper extremity, a left-sided hemi-hypoesthesia, a left-sided inferior quadrantanopia and a benign positional vertigo. Postural sense was normal in all extremities. No neuropsychological assessment was undertaken at that time.

Four to 5 months after surgery the patient suddenly noticed a "most peculiar feeling in the awareness of [her] body". She experienced it for the first time when walking her dog. The left half of her body was seemingly nonexistent, "not just feel numb or unresponsive to touch, but no longer present at all". This feeling of absence concerned both lower and upper limb and the left part of the head. It could be present for the leg alone, but never exclusively for the arm or the head. It was typically experienced when walking, could last for a few minutes up to an hour and was accompanied by vertigo and gait difficulties (no fall ever occurred). No sign of visual neglect seemed present, as ASG kept seeing the left side of her body, which puzzled her: "How can it be that I see something, whose absence I so convincingly feel?" ASG has never experienced any such episode while standing in front of a mirror. She has never seen other people's body incomplete. The paroxysmal feeling of an absent left half-body evoked some horror when first experienced, but the patient soon got used to it and the phenomenon lost its emotional impact. With a kind of amusement, she noticed that she was still able to lead her dog with the leash held by her left, "absent" hand. These episodes occurred several times a day (slightly more frequent in the evening compared to the morning hours) during at least 4 months. They then got spontaneously less frequent and receded by the feeling, over several weeks, of only the lower left body parts being felt as transiently absent. ASG spontaneously reported these experiences to her neurosurgeon; before, she had never talked to anybody else about them.

A neurological examination five months after surgery, i.e. when ASG was experiencing these episodes on a daily basis, produced results not different from the initial exploration, briefly after the operation. A routine neuropsychological examination revealed a general slowing in cognitive processing speed, which manifested itself in speed-sensitive attentional and executive tasks. Moreover, a mild to moderate deficit in verbal and non-verbal episodic memory was evident. The only signs of parietal dysfunction were slight problems in calculation and a mild left-sided inattention in isolated tasks on spatial exploration. Performances in tasks on language, visual perception and construction, praxis, mental rotation and executive functions were flawless. Used neuropsychological tests and the scores obtained by the patient are reported in Table 1.

Table 1. ASG's Neuropsychological performance. (with impaired performance highlighted in bold).

Function	**Test**	**Score (z-score)**
Attentional functions		
Alertness	TAP[1], Alertness	
- Median tonic alertness [ms]		**360 (-1.7)**
- Median phasic alertness [ms]		**287 (-1.2)**

Selective attention - Median [ms] - Errors - Omission error	TAP[1], Go/Nogo	 575 (-0.3) 1 (-0.3) **1 (-1.7)**
Divided attention - Median auditory [ms] - Median visual [ms] - Errors - Omission errors	TAP[1], divided attention	 **800 (-2.4)** **1234 (-2.5)** 2 (-0.7) **12 (-2.5)**
Information processing speed - Visuo-verbal [s] Color naming [s] Reading [s] - Psychomotor [s]	 D-KEFS[2] TMT-A[3]	 **43 (-2.0)** **37 (-2.7)** **80 (<-3.2)**
Memory span - Verbal - Visual	WMS-R[4]	 7 (-0.5) **6 (-1.5)**
Learning & Memory		
Verbal-episodic memory - Learning [words/max.] - Free recall [words/max.] - Recall [%] - Recognition [hits – false alarms]	HVLT-R[5]	 **15/36 (< -3.2)** **6/12 (-2.3)** 85 (-0.8) **7 (-2.7)**
Nonverbal-episodic memory - Learning [points/max.] - Free recall [points/max.] - Recall [%]	BVMT-R[6]	 **17/36 (-1.2)** **6/12 (-1.4)** **60 (-3.0)**

- Recognition [hits – false alarms]		**5 (-1.1)**
Executive functions		
Interference control	D-KEFS[2]	
- Speed [s]		**95 (-2.3)**
- Speed, relative [scaled value]		-1 (-0.8)
- Errors		1 (0.2)
Cognitive flexibility		
- Visuo-verbal	D-KEFS[2]	
Speed [s]		**105 (-1.7)**
Speed, relative [scaled value]		2 (0.7)
Errors		1 (0.2)
- Psychomotor	TMT-B[3]	
Speed [s]		**126 (<-3.2)**
Speed relative to TMT-A		1.47 (1.51)
Error		0
Fluency		
- Verbal phonematic [correct s-words]	RWT[7]	**11 (-1.7)**
- Nonverbal [correct]	H5PT[8]	19 (-1.0)
Working memory		
- Verbal	WMS-R[4]	8 (0.5)
- Visual	WMS-R[4]	**4 (-1.8)**
Visuo-spatial functions		
Visuoconstruction		
- Accuracy [points/max]	RCFT[9]	**25/36 (-2.5)**

- Speed [s]		**460 (-2.5)**
Questionnaires		
Depression	GDS[10]	28 (-1.0)
Fatigue		
- Physical	WEIMuS[11]	**23 (-2.8)**
- Cognitive	WEIMuS[11]	**27 (-3.2)**
- Total	WEIMuS[11]	**50 (-3)**

Note. [1] Test of Attentional Performance (Zimmermann & Fimm, 2002), [2]Delis-Kaplan Executive Function System (Delis et al., 2001), [3] Trial Making Test (Tombaugh, 2004), [4] Wechsler Memory Scale – Revised (Härting et al., 2000), [5] Hopkins Verbal Learning Test – Revised ((Brandt & Benedict, 2001), [6] Brief Visuospatial Memory Test – Revised (Benedict, 1997), [7] Regensburger verbal fluency test (Aschenbrenner et al., 2000), [8] HAMASCH 5-point-test (Haid et al., 2002), [9] Rey Complex Figure Test (Meyers & Meyers, 1995), [10] General Depression Scale (Hautzinger & Bailer, 1992), [11] Würzburger Fatigue Inventory (Flachenecker & Meissner, 2008).

Assessment of visuo-motor imagery

Approximately two months after the neuropsychological exam we assessed ASG's capacity of visuo-motor imagery for body parts in a computerized mental rotation task with hands and feet as visual stimuli (Parsons, 1987). These were depicted under four angles of rotation (0°, 90°, 180°, 270°; see Figure 2). Hands and feet were shown together within the same task once in volar, once in dorsal view. All stimuli (128 in total) were presented centrally on a laptop screen and spanned a visual angle of approx. 7° to 10° horizontally. ASG and controls were required to press a left-sided (right-sided) response key with her left (right) index finger on seeing a left-sided (right-sided) limb. Stimuli were displayed until a response was given. Accuracy and speed were equally stressed. Ten practice trials, which were not analyzed, preceded the task.

Feedback about response accuracy was provided exclusively during these practice trials. During the training phase a feedback on the correctness of the response appeared at the center of the screen. Stimulus presentation and response collection was programmed with the software E-prime 3.0 (Psychology Software tools, https://pstnet.com/products/e-prime/).

Ten age-matched controls (6 men, 4 women, mean age: 48.5, SD = 14.87) were tested with an identical procedure. ASG's performance accuracy was high (mean accuracy = 92.2%) and comparable to that of the controls (group mean accuracy = 90.47%, SD = 11.25%). Only reaction times (RTs) of correct decisions were analyzed. We compared ASG's RTs to those of the control group with the Bayesian inferential methods for use in single-case studies described in (Crawford & Garthwaite, 2007). This method proved robust for comparing one patient to a small control group. Data preprocessing and statistical analysis were performed in R studio v. 1.1.442. Crawford-Garthwaite Bayesian Test was performed with the function "Crawford.test" included in the R psycho v0.4.91 package (Makowski, 2018). The confidence interval bound was set at 95%. Significant threshold was set at 0.1 and the number of performed iterations was 10000. Data, stimuli, E-prime program and R scripts used for data analysis and visualization, and data can be viewed, reused and downloaded under this link: osf.io/qmkd3/.

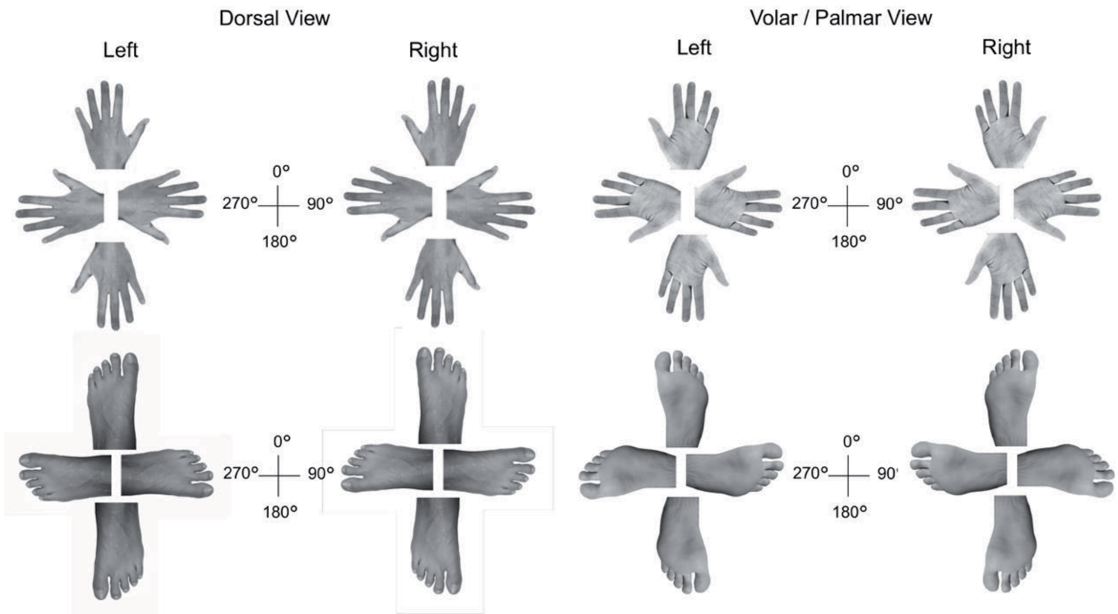

Figure 2. Overview of the hand (top) and foot stimuli (bottom) presented during the limb laterality task.

The study was approved by the Ethical Committee of the University of Zurich. After being informed on the purposes of the study, participants provided their written informed consent. The study was performed in according to the Helsinki Declaration (1964). Data, E-prime program, stimuli and R Scripts used for data analysis and visualization can be viewed, reused and downloaded under this link: osf.io/qmkd3/.

RESULTS

While being tested, ASG did not experience hemiasomatognosia. Nevertheless, analysis of her RTs to hands and feet under the different angles of rotation revealed that ASG was slower than control participants identifying specifically left feet displayed in volar view for the "comfortable" 90° postures (Crawford-Garthwaite Bayesian test, controls mean RT = 1797, SD = 532, ASG's mean RT = 5350, z = 6.68, percentile = 100.00, $p < 0.001$. ASG's RTs were higher than 99.99% (95% CI [99.99, 100.00]) of the controls' RTs). RTs to left feet displayed in volar view were also significantly slower in ASG for the "awkward" 270° postures (Crawford-Garthwaite Bayesian test, control sample mean RT = 2440, SD = 996, ASG's mean RT = 6670, $z = 4.25$, percentile = 100.00, $p < 0.01$. ASG's RTs were higher than 99.83% (95% CI [99.24, 100.00]) of the controls' RTs; see Figure 3). Furthermore, there was a significant "inversion effect" (longer RTs to stimuli under 180° than under 0°) for feet (Figure 4); crucially, for the difficult 180° stimuli, her RTs to *left* feet shown in dorsal views were significantly longer than those of control subjects (Crawford-Garthwaite Bayesian test, control sample mean RT = 2092, SD = 932, ASG's mean RT = 5710, $z = 3.88$, percentile = 99.99, $p < 0.01$. ASG's RTs were higher than 99.76% (95% CI [98.84, 100.00]) of the controls' RTs). None of the comparisons for right limb stimuli were significant ($p > 0.05$).

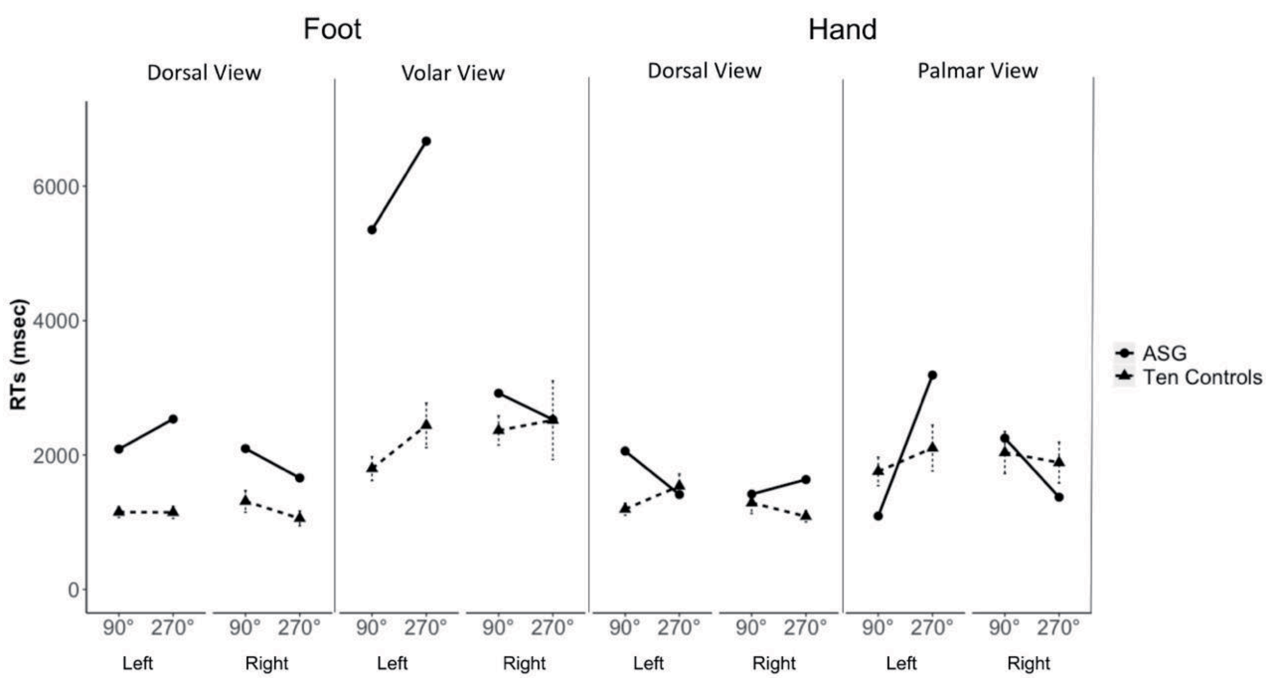

Figure 3. ASG' mean RTs (dots and thick lines) and ten control participants' mean RTs

(triangles and dashed lines; error bars indicate standard error of the mean) of correct decisions to left and right hands and feet, shown in dorsal and volar/palmar view at 90° and 270° of rotation.

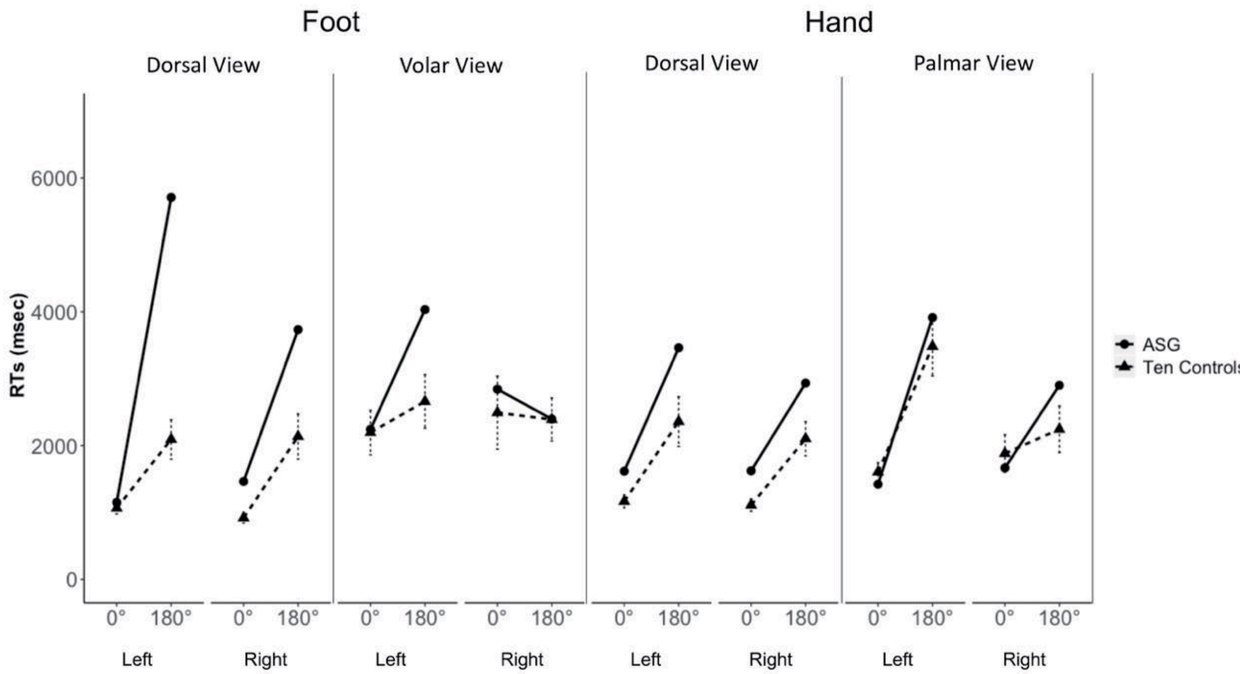

Figure 4. ASG' mean RTs (dots and thick lines) and ten control participants' mean RTs (triangles and dashed lines; error bars indicate standard error of the mean) of correct decisions to left and right hands and feet, shown in dorsal and volar/palmar view at 0° and 180° of rotation.

DISCUSSION

The structured interview introduced here (see Appendix) was used for the assessment of hemiasomagnotosia in patient ASG. She initially reported her paroxysmal experiences of left-sided hemiasomatognosia to the neurosurgeon. They were associated with vertigo, but never led to a fall (Bonnier, 1905). The feeling of nonexistence did not encompass a change in the feelings of ownership or of agency over the affected limbs. It was confined to the somesthetic domain, as ASG could still see her left body half (in contrast to cases with both somesthetic and visual asomatognosia (Stockert, 1934) or pure visual asomatognosia (Arzy et al., 2006). She also saw other people's body normal, i.e. did not project own symptoms onto others (Schilder, 1919).

ASG was administered a limb laterality judgment task thought to rely on the integrity of the participant's body schema. Body schema is the implicit and continuously updated representation of the position occupied by the limbs in the space and the biomechanical constraints arising from the sensory inputs, mainly proprioceptive and that access the motor system directly for the performance of routine motor acts (Head and Holmes, 1911). According to Parson's comparative method (Parsons, 1987), this task requires the activation of two processes. First, the selection of the representation of either the right or left limb and then the mental rotation maneuver of this representation to match the position of the depicted hand. The analysis of the RT may offer important insights into the disruption of one or the other process. For instance, previous studies showed that experimentally induced pain or expectation of pain to a hand leads to an increase in the RT that is specific for the non-painful limb. The interpretation of this effect is that an attention bias towards the painful limb, i.e., a marked difficulty in allocating the attentional resources away from it, induces a delay in the access to the non-painful limb representation (Hudson et al., 2006). On the other hand, longer RT specific for the painful hand was observed in patients with complex regional pain syndrome (CRPS; Moseley, 2004), which is characterized by a profound cortical reorganization and neglect-like sensory and exploration deficits reflected in the phenomenal experience that a "limb feels foreign" (Galer and Jensen, 1999; Förderreuther et al., 2004). Compatible with the performance of patients affected by CRPS, ASG's RTs to left, but not right, feet were slower than those of controls', specifically when presented under a motorically challenging degree of rotation (180°). We observed that ASG's accuracy did not statistically differ from that of the controls, suggesting an intact body schema. Since ASG presented with mild left-sided inattention on tasks of spatial exploration, we cannot exclude a causative role of attentional asymmetries in response to images of left and right limbs. However, the specificity of the impairment for RTs to left feet but not to left hands, suggests that while attentional asymmetries may contribute, they do not solely the present findings. Future studies should test patients with asomatognosia without neglect to specifically address this issue. Decisions to feet depicted in biomechanically awkward postures (270°) were slower than controls' for volar views but not for dorsal views. Previous studies showed that hands presented in palm view require the manipulation of the respective motor representation while hand in back view are more likely to be visually processed. While admittedly this view-dependent effect has not been explicitly tested for the mental rotation of feet, ASG's RT pattern for feet may reflect the type of left-sided hemiasomatognosia (no visual component), and we would predict a different pattern for patients with hemiasomatoscopy (visual hemiasomatognosia). However, whether view-dependent effects for feet analogous to those described for hands do in fact exist, needs to be established empirically in healthy research participants."In the only previous report of an asomatognosic patient's mental rotation of hands (Arzy et al., 2006), composite hand-arm pictures with either compatible or incompatible laterality were used as stimuli. These authors' patient was slower than controls in responding to the body part stimuli, whereas her mental rotation speed was comparable for letter stimuli. Patient ASG did not experience hemiasomatognosia at the time of solving the limb laterality task. Yet, compared to controls, her RTs were longer to some of the left-sided but to none of the right-sided limbs. That the RT differences were more obvious for foot stimuli than hand stimuli is in accordance with the observation that her asomatognosia had always been more pronounced for the leg compared to the arm and that it was still experienced for the lower limb when it no longer occurred for the upper. Also, the fact that ASG's RTs to left-sided body parts were significantly longer than controls' RTs under 180° rotation but not under 0° rotation, speaks against the assumption that there was an unspecific slowing for left-sided body parts. Rather, this difference seems to corroborate ASG's deficit in motor imagery. Our findings thus invite the use of limb laterality tasks to objectify an individual patient's symptoms of asomatognosia.

Our study comes with an important limitation. That is, ASG' s motor function for left upper and lower limbs were only clinically tested and judged normal. A formal assessment of the motor function is lacking. Alterations in the motor function of the upper and lower limb might have had an impact on the visuo-motor task. However while the responses for left-sided stimuli were given with the left hand, ASG's RTS were significantly slower for the stimuli requiring the mental rotation of a different effector, the left feet, making unlikely that impaired efferent processes might underly her impaired performance in the task.

It remains a challenge for future clinical studies to test patients with hemiasomatognosia repeatedly, once while feeling their body absent and once with a recovered, normal bodily awareness. Paradigms to experimentally induce asomatognosia in healthy volunteers may also prove revealing in clinical populations (Newport and Gilpin, 2011;,Stone et al., 2018).

Appendix: Structured interview

The template of the structured clinical interview is presented below

Ask any patient, who reports an absence or disappearance of the body or a feeling of amputation the following questions (to be adapted to the individual case):

(a) Where on the body

Which part(s) of the body appeared absent/amputated? Was the sensation of absence stronger/qualitatively different for some of these parts? Were always the same body parts affected? Can you provide a sketch of your body (front view and back view) and mark the affected parts? Please use different colors/shadings for phenomenally different impressions. (If patient is reluctant to draw a self-portrait, provide two simple sketches of a human body, once in back-vie and once in front-view).

(b) Triggering and modulating factors; modalities involved

On first occurrence, was there anything that may have triggered the experience?

Can the feeling of an absent body (part) be induced/modified by any factors?

Specifically, is the feeling of absence modulated by

- moving the affected body part(s)?

- having the affected body part(s) moved by somebody else?

- touching the affected body part(s) with one of your unaffected limbs (if possible)?

- having your affected body part(s) touched by somebody else?

- having your eyes open/shut?

- looking at the affected body part(s)?

- any other factor?

When you look at the body part you feel to be absent, do you still see it?

Have you ever experienced the absence of your body (parts)…

- … when in front of a mirror? (if yes, describe what happened to your mirror image, if anything)
- … when looking at other people's body? (if yes, describe any change you might have visually perceived)

Can you deliberately induce/abolish the experience?

(c) Frequency and time course

When was the first time you experienced an absence of your body? How many times have you had this experience since then? What is its daily (weekly / monthly) frequency? Is there a circadian pattern? How long does an episode usually last (provide minimal and maximal duration)? Do you still experience these episodes these days? Has their frequency been changing over the weeks (moths / years)? Has anything else been changing?

(d) Associated Symptoms

Was the feeling of nonexistence of your body (parts) accompanied by any other sensation or feeling? (regularly? occasionally?)

Has your consciousness been altered while experiencing the feeling of absence of your body (parts)? (expanded, dream-like, dizzy?)

Have you ever felt the subjectively absent body parts

- to belong to somebody else?

- to move/behave in ways that seemed not under your control?

- to be dead or rotting away?

- to be detached from the body and possibly present elsewhere?

Additional remarks

Questions should be adapted to the individual case, as a patient's initial description may be relatively precise (e.g. "it was as if I had lost any awareness of my left arm") or exceedingly vague (e.g. "I had some very peculiar experience concerning my body"). Adaptation is also required with respect to the clinical picture within the patient's asomatognosia is reported (e.g. whether there is an associated hemiparesis/hemiplegia, hemianopia, etc.). Once it has become clear to the examiner that the patient describes an episode of asomatognosia, phenomenal detail should be inquired, if possible by inviting free report while minimizing suggestive cues. The time course of the disturbances (and, if applicable, of single episodes) should be inquired, as (hemi)asomatognosia is commonly a long-term phenomenon (Sierra et al., 2002), and experiences in the second-range may suggest an epileptic origin (So & Schaüble, 2004). Questions unrelated to the core phenomenon of "bodily nonexistence" may uncover related perturbations of somatognosis and inform about the relative involvement of the somatosensory and visual modalities, respectively. The issue of perspective transformation is crucial in cases of asomatognosia associated with transitivism (Schilder, 1919; Wernicke, 1906), i.e. the projection of own symptoms onto other persons. Will a patient who lacks awareness of her left side see other persons' left or right side absent? The answer depends not only on lesion location, but will be revealing about the relationships between body, self, and phenomenal space (Peter Brugger, 2002).We recommend to video-tape the entire interview after having obtained the patient's written informed consent. A sketchy self-portrait, which depicts affected body regions may also be helpful, preferably on a back-view and a front-view sketch of a human body. Needless to say that the interview should be complemented by a comprehensive neuropsychological evaluation. In cases of unilateral asomatognosia, testing different forms of hemispatial neglect are especially important.

STUDY 4. PHANTOM LIMB SENSATION I

Gaze, behavioral, and clinical data for phantom limbs after hand amputation from 15 amputees and 29 controls

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ABSTRACT

Despite recent advances in prosthetics, many upper limb amputees still use prostheses with some reluctance. They often do not feel able to incorporate the artificial hand into their bodily self. Furthermore, prosthesis fitting is not usually tailored to accommodate the characteristics of an individual's phantom limb sensations. These are experienced by almost all persons with an acquired amputation and comprise motor and postural properties of the lost limb. This article presents and validates a multimodal dataset including an extensive qualitative and quantitative assessment of phantom limb sensations in 15 transradial amputees, surface electromyography and accelerometry data of the forearm, and measurements of gaze behavior during exercises requiring pointing or repositioning of the forearm and the phantom hand. The data also include acquisitions from 29 able-bodied participants, matched for gender and age. Special emphasis was given to tracking the visuo-motor coupling between eye-hand/eye-phantom during these exercises.

INTRODUCTION

Following hand loss, dramatic changes in an individual's daily life can occur. Hand amputees often struggle to accomplish several everyday activities and many of them are destined to social isolation and unemployment(Andresen et al., 2016; Niedernhuber et al., 2018). This may be partly explained by the self-reported lack of feeling and acceptance of a prosthesis as one's own limb (Collins et al., 2017) or of embodiment, as described by "*the ability to process information through external objects at the sensory, motor and/or affective levels in the same way as the properties of one's own body parts"* (Makin et al., 2017). Of crucial, yet largely neglected importance in designing high-tech prostheses is their interaction with phantom limb sensations (PLS), that is, the continuous phenomenal presence of sensory, motor and postural aspects in the missing body segment (Peter Brugger, 2006).

PLS are felt by up to 95% of the amputees, with variable onset and duration (V. S. Ramachandran & Hirstein, 1998). They can be experienced as painful (e.g., burning, cramping, stabbing) or non-painful. Previous studies are often biased towards *painful* PLS. Wearing a functional prosthesis is generally considered to reduce pain (Lotze et al., 2001). However, with regard to non-painful PLS, some clinicians consider them a source of interference that hinders the successful incorporation of a prosthesis into the body schema (Mayer et al., 2008). Other authors rather emphasize that the vivid presence of a PLS may facilitate the dexterous use of an artificial limb(Powell et al., 2014;, Atzori et al., 2016). PLS are generally localized in the extracorporeal space, beyond the visible anatomical borders of the residual limb. Prostheses and artificial limbs are physical matter that can overlap the phenomenal space of a phantom limb. When this happens, approximately 50% of amputees still feel their phantom limb – if only in superposition with physical matter. In the other 50%, the phantom limb disappears or is withdrawn within the stump (Jalavisto, 1950). We recently proposed the definition of Obstacle Tolerance (OBT) and Obstacle Shunning (OBS) for these two fundamentally different types of behaviour (Saetta et al., 2018). Only a few clinical observations document this interaction between mind and matter (Jalavisto, 1950; Saetta et al., 2018). However, the characterisation of this interaction appears crucial, as it might represent a key predictor of how fast and how satisfactory the embodiment of a prosthesis may take place.

This article presents independent datasets that include gaze, surface electromyography (sEMG), accelerometry as well as behavioral data from exercises conducted within the MeganePro project (Myo-Electricity, Gaze and Artificial-intelligence for Neurocognitive Examination & Prosthetics), an interdisciplinary and multicenter project which aimed at i) improving the control of myoelectric hand prosthesis and ii) understanding the neurocognitive alterations and clinical parameters in hand amputees.

The first aim of MeganePro is addressed in our parallel contribution presenting the MeganePro dataset 1 (MDS1). MDS1 refers to exercise 1, examining grasping movements using gaze and computer vision. (Cognolato et al., 2020)

The present contribution addresses the second MeganePro aim and presents MeganePro dataset 2 (MDS2 - Saetta et al., 2019a), MeganePro dataset 4 (MDS4 – Saetta et al., 2019b) and MeganePro dataset "Clinical Interview and Neurocognitive Tests in Amputees" (MDSInfo - Saetta et al., 2019).

MDS2 contains the multimodal data for exercise 2, which tapped into the eye-hand coordination in able-bodied subjects and eye-phantom coordination in amputees during motor imagery (MI) and motor execution (ME) of visually-guided pointing movements. Fitts' law (Fitts, 1954) describes the speed-accuracy trade off when aiming with constant accuracy to point to an ever smaller target area: the total movement duration is inversely related to the logarithm of the target width. Such speed-accuracy effects were previously exploited for assessing the dexterous use of myoelectric prostheses. While in Bouwsema et al.(2012) kinematics and a few clinical measures were collected, in a more recent study (Sobuh et al., 2014), visuo-motor behaviour was analysed adopting a visually-guided pointing paradigm. Here, we recorded multimodal data that can be analysed with reference to a participant's individual experience of PLS.

MDS4 contains the multimodal data for exercises 4 and 5. These exercises systematically study OBS and OBT. The hand/phantom is repositioned from a starting to an end point in the presence of hindering physical matter, an "obstacle", in between these points. To the authors' knowledge, no previous literature has attempted to quantitatively characterize phenomena that are otherwise only clinically observed and described with self-report measures.

The dataset MDSInfo contains clinical and behavioral tests that are sensitive to detect multiple attributes that define a phantom limb, including OBS and OBT, and to provide scores of developments over time, intensity, frequency, vividness and emotional connotations for each attribute. Other meaningful phenomena such as motor imagery, i.e., the capacity to evoke a movement without the overt action (Jeannerod & Decety, 1995), and the impact of the amputation condition on an individual's quality of life are also reported. Thanks to this dataset, neurocognitive alterations and clinical parameters of PLS can be analysed in relation to the performance to all the exercises.

The analyses presented in this article validate the procedures and illustrate the usefulness of the data for a broader community of researchers in both prosthesis design and in the psychological and neuroscientific sequelae of hand amputation.

METHODS

Participants

Fifteen transradial hand amputees (13 men, 2 women, mean age: 47.13 ± 14.16 y; mean years since amputation: 9.5 ± 8.5) and 29 able-bodied controls (26 men, 3 women, mean age: 47.31 ± 15.18) participated in the study. Out of the amputees, 47% were using a myoelectric prosthesis (mean hours/day: 10.06 ± 5), 33% were using a cosmetic prosthesis (mean hours/day: 7.2 ± 3.6), and 20% were using a body-powered one (mean hours/day: 13.3 ± 3.6). All amputees experienced non-painful PLS with high interindividual variability in terms of onset, intensity and frequency. About 73 % of the amputees reported painful PLS. Shrunk sensations were observed in 60% of them. About 86% of the amputees could freely move the phantom, while the other 13% of the amputees reported the feeling of having the phantom limb stuck in a certain position, i.e. frozen phantom (L. Collins et al., 2018). This was tested by asking the participants to perform phantom finger tapping and phantom fist movements. OBS and OBT were observed in 46% and 54% of amputees. The OBS and OBT groups did not statistically differ in age ($p = 0.37$) nor years since amputation ($p = 0.23$) as tested by a two-samples t-test. Of all fifteen participants, eight dreamed about themselves as able-bodied, two as amputated, and a mixed pattern was observed in one amputee. Two amputees were not able to remember their dreams. One amputee could not recall the dreams vividly. Body representation in dreams is not available for one participant because of language barrier during data collection. Referred sensations were reported in 40% of the amputees. Table 1 displays an overview of the demographical and clinical parameters presented above. For the information relative to able-bodied controls, we invite the reader to see Table 1 in Cognolato et al. (2020).

Table 1. Overview of amputees' clinical and demographical characteristics

ID	Sex	Age	Most used prosthesis	Use of prosthesis (Hours/Day)	Painful PLS	Non painful PLS	Shrunk	Frozen Phantom	Ostacle Shunning or Tolerance	Body Representation in Dreams	Referred Sensation
101	Male	52	Cosmetic	8	YES	YES	YES	NO	OBT	Intact limb	YES
102	Male	39	Cosmetic	9	YES	YES	YES	NO	OBS	Mixed	NO
103	Male	63	Myo-open-close	15	YES	YES	YES	NO	OBS	No dreams at all	NO
104	Male	49	Myo-open-close	9	YES	YES	YES	NO	OBT	Intact limb	NO
105	Male	73	Body-powered	16	YES	YES	YES	YES	OBT	Not vivid dream recall	NO
106	Male	70	Body-powered	8	YES	YES	NO	NO	OBT	Intact limb	NO
107	Male	36	Body-powered	16	YES	YES	YES	NO	OBT	Intact limb	NO
108	Male	35	Myo-open-close	16	YES	YES	YES	NO	OBS	No dreams at all	NO
109	Male	65	Cosmetic	8	YES	YES	NO	NO	OBS	Intact limb	YES
110	Male	38	Myo-open-close	9	YES	YES	NO	NO	OBS	Intact limb	NO
111	Male	38	Myo-open-close	5	NO	YES	YES	YES	OBT	Language barrer	YES
112	Female	33	Cosmetic	10	NO	YES	YES	NO	OBT	Amputated limb	NO
113	Male	28	Myo-open-close	4.5	NO	YES	NO	NO	OBS	Amputated limb	YES
114	Male	52	MYo-open-close	16.5	NO	YES	NO	NO	OBT	Intact limb	YES
115	Female	36	Cosmetic	1	YES	YES	NO	NO	OBS	Intact limb	YES

Ethical Requirements

Participants were provided with a written and oral explanation of the procedure and gave the signed informed consent form as a first step. One of the participants expressed his consent to publish identifiable images by filling in a form.

The experimental protocol, configured as a multi-center study, complies with the principles expressed in the Declaration of Helsinki (1964) and it was approved by the Ethics Commission of the Province of Padova in Italy (NRC AOP1010, CESC 4078/AO/17) and the Ethics Commission of the Canton of Valais in Switzerland (CCVEM 010/11).

ACQUISITION SETUP

MDS2 and MDS4

The acquisition setup designed for exercises 2, 4 and 5 included acquisition hardware and software specifically developed for recording gaze, video in the participant’s first-person perspective, sEMG, accelerometer as well as behavioral data from multiple devices. The acquistion software included a backend, a media player, a text-to-speech engine, and a graphical user interface. The backend was developed in C++ and its primary objective was to acquire the data from the different devices and store them in the laptop with as low latency and number of packets lost as possible. Furthermore, the backend applies a high-precision timestamp to the recorded data. These timestamps allow to synchronize the modalities during the post-processing step.

Vocal instructions synthesized by the text-to-speech engine guided the participant through the trails of the exercise. This solution allowed us to maintain a high quality testing environment, as it does not introduce any visual distractions that may have biased the users' gaze behavior. In addition, the instructions were prepared in Italian, English, French, and German, covering the languages spoken by all the participants. A graphical user interface was also included and allowed the experimenter to handily interact with the software and conduct the experiment.

Gaze and first-person perspective videos were collected with the Tobii Pro Glasses 2 (Tobii AB, Sweden, http://www.tobiipro.com/). This device is a lightweight, portable, and unobtrusive eye tracker equipped with a Full HD camera, an Inertial Motion Unit (IMU), and a microphone. The Tobii Pro glasses (Tobii AB, Sweden) can be worn in the same manner as standard glasses and various nose pads can be chosen to guarantee the best tracking and comfort. Furthermore, corrective lenses can be applied in case of users with a visual impairment. The device includes a recording unit to which the glasses are connected. The recording unit provides the power supply through a rechargeable battery, stores the data into an SD card, and can communicate wirelessly with other devices (e.g., a personal computer). The Tobii Pro glasses (Tobii AB, Sweden) allowed to measure the gaze position with respect to the first-person perspective video recorded by the scene camera. The gaze point was then overlapped onto the scene camera video locating where participants were looking. The Tobii Pro glasses (Tobii AB, Sweden) also returned an estimation of the gaze position in three-dimensional coordinates, the position and diameter of the pupils, as well as the acceleration and the angular velocity of the participant's head.

Muscle electrical activity and inertial data were recorded with a Delsys Trigno Wireless sEMG system (Delsys Inc., USA, http://www.delsys.com/). This device is equipped with 16 electrodes that communicate wirelessly with a base station. Four silver bar contacts allow each electrode to record the EMG signal at skin level. In addition, a triaxial accelerometer is embedded in each electrode. The base unit receives the data streamed by the electrodes with a sampling rate of 1926 Hz for the EMG and 148 Hz for the accelerometer. We set the accelerometer range to ± 1.5 g. For this range, a noise of 0.007 g (RMS), and an offset error of $\pm$ 0.201 g for the X and Y axes and 0.201 g to -0.343 g for the Z axis are reported. These data can then be accessed via a personal computer connected to the base station. For a more detailed description of the acquisition software and most of the devices used in the present study see Cognolato et al (2020).

Moreover, a footswitch was employed to collect the time to completion of a trial. The footswitch was connected to the acquisition laptop via USB and used as an additional keyboard. Thus, participants were able to autonomously input events into the acquisition software by pressing the footswitch. This solution let the participant free to focus on the execution of the exercise and fostered a natural upper limb movement. A footswitch was preferred over manually provided keypresses as it ensures the absence of any contamination of the MI and ME of the upper limbs by a motor response with the same effector, as they did for example in Gallo et al. (2018).

The acquisition setup specifically for exercise 2 (MDS2) consists of five target squares, referred to as *pointing targets*, and a rectangular target. The pointing targets consisted of red squares of various sizes printed on the center of transparent sheets. They served as target for the (imagery) pointing movements to be performed with the tip of a pen. The side of the red squares were 1.25 mm, 2.5 mm, 5 mm, 10 mm , and 20 mm, in line with a previous study(Sirigu et al., 1996). The delimiting target, indicating the starting point of the movement, was a black rectangle printed on a transparent plastic sheet. The center of the smallest pointing target was aligned to the participant's body-midline and was fixed at a distance of 47 cm from the border of the table. The starting point of the (imagery) movements, marked with the delimiting target, was horizontally aligned with the pointing target at a distance of 32.6 cm (see Figure 1).

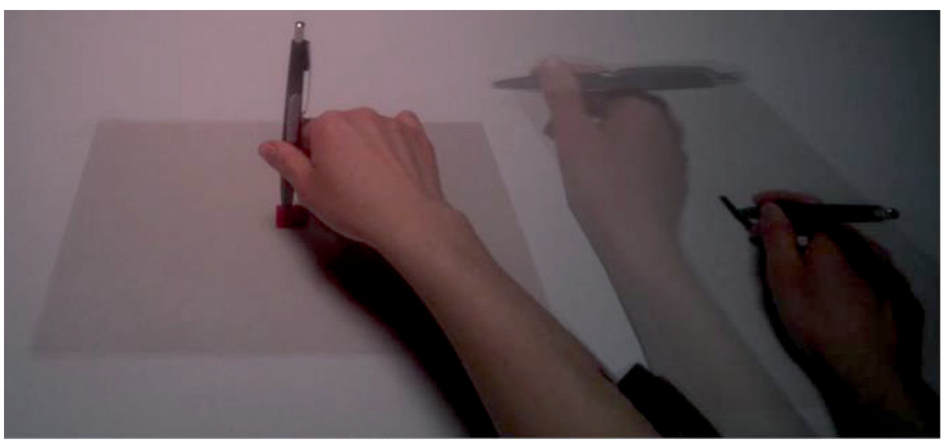

Figure 1Acquisition setup for exercise 2 and the movement performed to point the target with the tip of the pen. The red square in the middle of the scene and the black rectangle on the right of the scene represent the pointing and delimiting targets, respectively.

The acquisition setup specific for exercises 4 and 5 (MDS4) consists of an obstacle and two delimiting targets. The obstacle was a wooden rectangle box of dimensions (H x W x L) 26 x 16.5 x 31.7 cm. This item was aligned with the participant body's midline at a distance from the border of the desk that was considered comfortable by the participant. The two delimiting targets indicated where the movement had to begin and finish. These targets were placed at 13 cm from both the left and the right side of the obstacle (see Figure 2).

Figure 2. Acquisition setup of exercises 4-5 and the sequence of movements performed to reposition the (phantom) hand. The start and end points were delimited by black squares. a) exercise 4: The participants are required to move the hand/stump around and above the obstacle. b) exercise 5: The amputees are asked to move the stump in a way that the phantom would pass through the obstacle.

MDSInfo

Demographic and clinical information such as sex, age, weight, height, body mass index, laterality of amputated hand, reason of amputation, years since amputation, type of used prosthesis specifying the hours per day and the most used prosthesis at the time to data acquisition are provided. All amputees underwent the clinical interview and cognitive tests in Italian according to their own and the examiners' mother tongue, except in one case described in the usage notes.

The tests were administered by trained neuropsychologists and incorporate published and well-established structured tests and interviews. An extended table reporting the scores of each item of the interviews and the instructions for decoding the scores can be found in MeganePro Participants information Dataset (MDSinfo - Saetta et al., 2019).

Handedness

The amputees' hand preference for skilled activities prior to amputation was assessed by means of the FLANDERS questionnaire (Nicholls et al., 2013), which lists 10 skilled activities and provides a score which indicates left, right or ambidextrous hand preference.

Painful and Non-Painful Phantom Limb Sensations

The "*Phantom and Stump Phenomena Interview*"*(PSPI* - Winter et al., 2001)*)* was administered. It starts with the characterization of painful PLS and checks the presence of 18 pain descriptors (e.g., the pain is burning, gruelling, or exhausting), that partly overlap with those presented in the McGill Pain Questionnaire-2 (Dworkin et al., 2009;, Flor et al., 1995). For the specification of the pain descriptors and all the single items we invite the interested reader to inspect the extended table in the MDSinfo (Saetta et al., 2019).

Detailed reports are presented on intensity and frequency of painful PLS (computed as the ration intensity/frequency, according to Lyu et al.(2016)). Duration of these PLS was protocolled as well and the type (and effectiveness) of a treatment, if applicable. The strategies a patient may have adopted to reduce pain and the extent to which the patient could benefit from them were also inquired, as well as environmental and emotional factors that can increase or decrease the pain. The same detailed questions were also asked with respect to non-painful PLS and residual limb sensations. They comprise, among others, length, girth, position in space and changes over time, spontaneous vs. intentional movement of the phantom hand and temperature sensations. For each attribute, scores of intensity, frequency and magnitude are given in the dataset. Shrinkage and elongation of the phantom are also reported in terms of onset, intensity, frequency and changes over time.

Body Representation in Dreams

The PSPI also includes a section on body representation in dreams. The way an amputee represents him/herself in dreams have been taken as an implicit index of distress during the waking state and was found to be associated with specific aspects of PLS (Bekrater-Bodmann et al., 2015; Brugger, 2008).

Referred sensations

The PSPI was slightly extended to describe presence and intensity of referred sensations, that are, sensations localized to the phantom hand after a tactile stimulation of a remote zone of the amputee's body ("trigger zone"). In accordance with the literature (Peter Brugger, 2006), the most common trigger zone is the participant's face. The investigation of referred sensations has proven important. Indeed previous studies showed that the successful embodiment is associated with the referral of sensation to the prosthesis.

Obstacle Shunning and Obstacle Tolerance

The "*Structured Interview on Phantom Sensations"*(Peter Brugger et al., 2000) was particularly useful for the assessment of Obstacle Tolerance versus Obstacle Shunning. OBT and OBS are measured in the following way: the amputee is asked to slowly approach the stump to a wall and indicate, qualitatively and quantitatively, any changes relative to the baseline vividness of the phantom limb. Two further tests require the participant to give a similar rating, but not upon approaching a wall, but instead on approaching the examiner's body and, finally, the amputee's own body. A distinction between OBS and OBT in relation to the nature of the physical matter (non-biological vs. biological) seems desirable, as the different forms could be predictive of different aspects of a prosthesis (embodiment vs. use in social contexts).

Impact of the Amputation on the Quality of Life

Special attention is paid to the functional impact of the amputation on the amputee's daily life activities as assessed by the *"Disabilities of the Arm, Shoulder and Hand questionnaire"* (Gummesson et al., 2003) adapted for hand amputation. Patients were asked to rate their ability to perform daily life activities on a 5-point Likert scale.

Motor Imagery

The questionnaire "*Vividness of Movement Imagery Questionnaire-2 – VMIQ2*" (Roberts et al., 2008) was used to inquire a participant's MI capabilities in different modalities, namely kinaesthetic and visual. The section on visual MI considers two different visual perspectives: (i) an external one, where participants are explicitly asked to watch themselves performing the movements from an external point of view, thus adopting a third person perspective; (ii) an internal visual imagery condition, where a first-person perspective has to be taken. The VMIQ2 was administered to both amputees and able-bodied participants. Versions adjusted to a participant's native mother tongue were used.

ACQUISITION PROTOCOL

MDSInfo

After signing the informed consent form and having provided demographical data, amputees and able-bodied controls underwent the clinical interview and neurocognitive tests. During both the tests and clinical interview, amputees were not wearing their prostheses. For amputees the order of administration of the tests was the following:

(i) "*Flanders questionnaire*", (ii) "*Phantom and Stump phenomena Interview",* (iii) *"Structured interview on Phantom Sensations"*, (iv) *"Disabilities of the Arm, Shoulder and Hand Questionnaire",* (v) "*Vividness of Movement Imagery Questionnaire-2 – VMIQ2*".

The clinical interview was conducted before the beginning of the exercises described in this manuscript but after the completion of exercise 1 (Cognolato et al., 2020). This allowed participants to rest between the exercises in order to prevent muscular fatigue on the residual limb.

MDS2 and MDS4

The exercises were conducted with the participant comfortably sitting in front of a desk. A Delsys Trigno electrode was positioned on each forearm. When possible, the sensors were placed at the level of the e*xtensor digitorum superficialis,* identified by palpation. This was not a strict requirement as in this experiment the inertial data were considered of paramount importance, while the sEMG would serve for control analyses. The participant wore the Tobii Pro glasses (Tobii AB, Sweden) and the examiner placed the footswitch beneath the desk in a position that allowed the participant to comfortably press it with the foot. As a last step, the examiner arranged the items on the desk as described in the Acquisition Setup section.

MDS2. Exercise 2: Visually-guided Pointing

During this experiment, participants were told to perform pointing movements with the tip of a pen from a starting location to the target (see Figure 1). Participants underwent a training where they were told to point with the tip of a pen from the black rectangle to the red squares with horizontal and natural movements. Afterwards, they were asked to imagine pointing movements without executing them and to use a motor strategy (rather than a visual one) to solve the exercise, that is, evoking the kinaesthetic and motor information. Participants were also instructed to press the pedal at the beginning and at the end of the training session trials. Speed and accuracy were equally stressed. Able-bodied controls underwent the training using their dominant hand, amputees used both their intact and phantom hands.

The experimental MI and ME blocks consisted of 8 cycles for each of the 5 pointing target dimensions, resulting in 40 trials each. The order of the presentation of the trial was randomized. A vocal instruction invited the participant to start the trial. The start and end of a trial were indicated by the participants themselves by pressing the footswitch located beneath the table. The behavioral outcome, namely the time to completion, was defined as the interval between two pedal presses. We measured the time to completion of one single pointing movement. Amputees underwent three pseudorandomised blocks: i) MI of the phantom limb, ii) MI of the intact hand, and iii) ME of the intact hand. For the able-bodied participants, these blocks were 2: i) MI and ii) ME of the dominant hand. The MI blocks always preceded the ME ones (Sirigu et al., 1996).

MDS4. Exercise 4: Obstacle Shunning. Hand/Phantom Limb Repositioning by Moving Above an Obstacle

In exercise 4, participants were asked to imagine or reposition a (phantom) hand from point A to B passing *around and above* an obstacle (see Figure 2, left panel). The most distal segment of the amputees' residual limb was aligned horizontally with the side of the obstacle which was aligned to the body midline. One trial consisted of three times moving from point A to B and then back to point A. For the amputees, the paradigm included 4 pseudorandomized blocks, each comprising 8 trials: i) MI of the phantom limb, ii) ME of the phantom limb which required to move the stump, iii) MI of the intact hand, iv) ME of the intact hand. For able-bodied participants the exercise also comprised 4 blocks: MI and ME of each of the two hands.

MDS4. Exercise 5: Obstacle Shunning. Phantom Limb Repositioning by Moving Through an Obstacle

Exercise 5 was performed in only 11 out of 15 amputees because it was conceptualized only after testing the first 4 amputees. Here, behavioral, gaze and muscular patterns were measured while the phantom progressively invades the space occupied by an obstacle. The experimental paradigm and setup are the same as in the exercise 4. However, amputees were asked to reposition the phantom from a point A to a point B passing *through* the obstacle (see Figure 2, right panel). Two blocks of 8 trials each were implemented for imagery and real execution of the phantom movements.

POST-PROCESSING

Throughout the exercises, the acquisition devices described previously recorded raw data to files stored on disk. We developed a processing routine in MATLAB (MathWorks, Natick, MA, USA, http://www.mathworks.com/) to perform data curation (for instance by verifying the absence of acquisition errors), to synchronize the individual modalities and finally to store them in a single unified data file. This section briefly outlines the processing procedure; for a more detailed description the reader is referred to Cognolato et al. (2020)

After the acquisition ended and prior to any further processing, repetitions not correctly performed were manually invalidated. The most common mistake was a delayed press of the footswitch due to a variety of reasons, which would have been hardly identifiable in post-processing.

The first step of automated processing then involved reading the acquisition files one by one and converting them in meaningful data structures. For all modalities, we made corrections to the recorded timestamps to bring them in a shared reference time. Since sEMG and accelerometry were sampled in batches for computational reasons, their timestamps were interpolated to obtain an individual timestamp for each sample. Furthermore, the sEMG data were filtered from outliers and powerline interference, and then rectified via a moving root-mean-square with a window length of 300 samples (approximately 156 ms). Separate types of information from the Tobii Pro glasses (Tobii AB, Sweden) were grouped together if it had been measured at the same time (i.e., they were assigned an identical timestamp).

We subsequently synchronized all modalities by re-sampling each of them to the sampling rate of the gaze modality. The re-sampling was implemented via linear interpolation for real-valued signals and nearest-neighbor interpolation for discrete signals. If an acquisition was interrupted and therefore consisted of more segments, then these were concatenated at the exact point that would avoid duplicated trials. As a final part of the processing pipeline, identifying information was removed from all videos.

DATA RECORDS

The data acquired and processed according to the procedures described above were released in two datasets on Harvard Dataverse, one for one for exercise 2 (MDS2) and one for exercises 4 and 5 (MDS4)[15]. The data from the clinical Interview and neurocognitive tests were also stored in a dedicated dataset (MDSInfo).

MDS2

The dataset for exercise 2 is available in the MeganePro MDS2 (MDS2 - Saetta et al., 2019a). It contains two data files in MATLAB (MathWorks, Natick, MA, USA) format for each intact participant, namely the motor and imaginary parts of the exercise. The MeganePro MDS2 (MDS2 - Saetta et al., 2019a) comes with the DatasetContentCRC.sfv file that reports the dataset structure and the Cyclic

Redundancy Check (CRC) value of each file. The DatasetContentCRC.sfv file can be used to check the appropriateness of the downloaded data and to have an overview of the dataset structure. For amputated participants, there is an additional data file for the exercise when executed with the stump. The filename of each file clearly specifies the participant's ID and the experimental setting. The common fields in all data files are reported in Table 2. The target field contains integers from 1 to 5 that indicate in increasing order the targets of 1.25 mm, 2.5 mm, 5 mm, 10 mm, and 20 mm. For each of the participants and experimental settings we also release the video from the first-person perspective encoded with MPEG-4 AVC in an MP4 container[13].

Additional information on the properties of the fields are:

- The field *emg* contains the sEMG signals recorded with the Delsys Trigno electrodes. It is composed of two columns, reporting the signals recorded by the electrodes on the right and left forearm or residual limb, respectively.

- The field *acc* contains the accelerometer data of the Delsys Trigno electrodes. The structure is the same of the *emg* field but with the acceleration values of the X, Y, and Z axes of the two electrodes. Due to the placement of the electrodes, the reference system of the accelerometer has the X axis parallel to the subject's forearm, the Z axis orthogonal to the subject's forearm, and the Y axis tangent to the forearm circumference.

- The gaze point position relative to the video-frame is reported in the *gazepoint* field. The position is expressed in (x,y) coordinates and their center is located on the top left corner of the video-frame.

- The fields *gazepoint3D, pupilcenterleft, pupilcenterright, gazedirectionleft, and gazedirectionright* are reported in (x,y,z) coordinates. The coordinates are relative to the reference system of the scene camera, which has its origin in the center of the camera, the X axis points to the subject's left, the Y axis points upwards, and the direction of the Z axis follows the right hand rule. The unit vectors *gazedirectionleft* and *gazediretionright* have origin in the left and right pupil centers, respectively.

- *The tobiigyr* and *tobiiacc* fields contain the angular velocity and the acceleration of the Tobii glasses in the X, Y and Z axes.

MDS4

The data for exercises 4 and 5 are available in the MeganePro MDS4 (MDS4 - Saetta et al., 2019b) and similarly structured. For each participant, a MATLAB (MathWorks, Natick, MA, USA) data file and the corresponding MP4 video registration file are available. For those participants who also performed exercise 5, an additional data file and MP4 video that is marked as ex5 are available. The fields in these data files are shown in Table 2, whereas the interpretation of the type identifier field is instead given in Table 3.

Table 2. Common fields in all the data files and specific stimulus fields for exercise 2.

Field	Dim	Units	Description
acc	6	g	3-axis acceleration of the 2 electrodes
emg	2	V	myoelectric activity of the 2 electrodes
pedal	1		indicator for the pedal presses

gazepoint	2		2D gaze point relative to the scene image
gazepoint_invalid	1		invalidity indicator for "gazepoint"
gazepoint3D	3	mm	3D gaze point in world coordinates
gazepoint3D_invalid	1		invalidity indicator for "gazepoint3D"
gazedirectionleft	3		3D gaze direction of the left eye
gazedirectionleft_invalid	1		invalidity indicator for "gazedirectionleft"
gazedirectionright	3		3D gaze direction of the right eye
gazedirectionright_invalid	1		invalidity indicator for "gazedirectionright"
pupilcenterleft	3	mm	3D position for the pupil center of the left eye
pupilcenterleft_invalid	1		invalidity indicator for "pupilcenterleft"
pupilcenterright	3	mm	3D position for the pupil center of the right eye
pupilcenterright_invalid	1		invalidity indicator for "pupilcenterright"
pupildiameterleft	1	mm	pupil diameter of the left eye
pupildiameterleft_invalid	1		invalidity indicator for "pupildiameterleft"
pupildiameterright	1	mm	pupil diameter of the right eye

pupildiameterright_invalid	1		invalidity indicator for "pupildiameterright"
tobiiacc	3	m s^{-2}	3-axis acceleration of the Tobii
tobiiacc_invalid	1		invalidity indicator for "tobiiacc"
tobiigyr	3	° s^{-1}	3-axis angular velocity of the Tobii
tobiigyr_invalid	1		invalidity indicator for "tobiigyr"
tobiits	1	s	timestamp in the Tobii clock
vts	1	s	MP4 video timestamp
mp4videoidx	1		counter for the MP4 video
pts	1	s	TS presentation timestamp
tspipelineidx	1		TS pipeline ID
tsvideoidx	1		counter for the TS video
ts	1	s	timestamp in the computer clock
target	1		ID of the target size
repetition	1		repetition counter
type	1		ID of the experiment type
repetition	1		repetition counter

Table 3 Interpretation of the type identifier for exercises 4-5.

ID	Description
1	Imagined Right
2	Motor Right
3	Imagined Left
4	Motor Left
5	Imagined Stump
6	Motor Stump

MDSInfo

The questionnaire is published as part of the data of exercise 2 in MeganePro Participants information Dataset (MDSinfo - Saetta et al., 2019). This file is published as a Microsoft Excel spreadsheet in the "xlsx" format. The first worksheet in this file contains all responses from all participants, with participants organized on rows and their responses in columns. The interpretation of each column is detailed in a second worksheet.

TECHNICAL VALIDATION

MDS2 and MDS4

Error Validation of Gaze Data

We added a calibration assessment at the beginning and end of nearly all the exercises to validate the quality of eye-tracking. Overall, we found an accuracy and precision of -0.8 +/- 25.8 pixels and -9.9 +/- 33.6 pixels on the horizontal and vertical axes, respectively. These values correspond to a real-world precision and accuracy of approximately -0.4 +/- 11.5 mm and -4.4 +/- 14.9 mm at a distance of 0.8m. For a more in-depth description of these values, the interested reader is referred to the work in Cognolato et al. (2020).

Correspondence between Motor Imagery and Motor Execution

The first analysis aimed at ensuring for all the exercises that participants were not moving the limb and/or the stump in the MI as compared to the ME condition. For this, we used the measurements of the accelerometers on each arm. We calculated the magnitude of acceleration for each sample. This magnitude varies with (translational) changes in acceleration of the arm, whereas it measures a constant value if the arm is static (i.e., only the constant gravity acceleration). The standard deviation of this signal within an experimental block thus indicates the amount of movement. The median movement measure is generally lower in MI than in ME both in amputated and able-bodied groups and for all the exercises (see Figure 3 for the exercise 2 and Figure 4 for exercises 4-5), confirming that MI and ME were correctly performed.

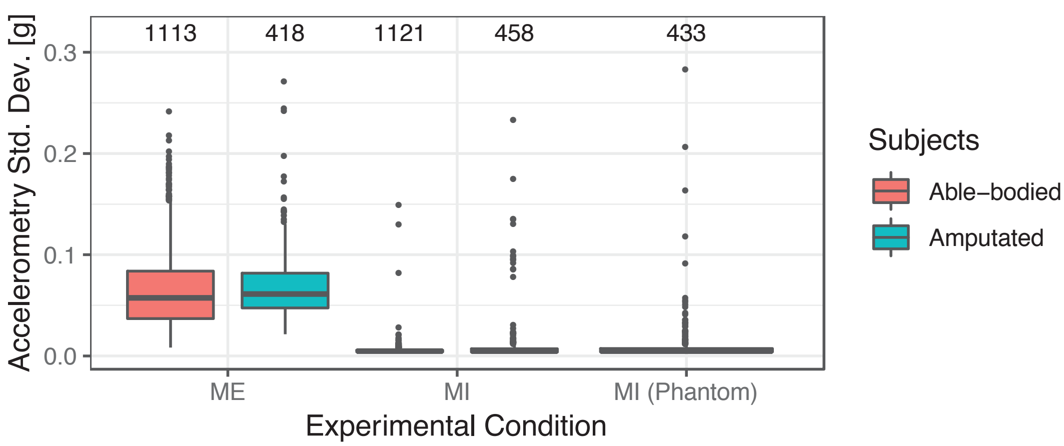

Figure 3. Standard Deviation of the acceleration magnitude of the arm in exercise 2 for motor imagery (MI) and motor execution (ME) of pointing movements. Able-bodied individuals used the dominant hand for both MI and ME conditions. Amputees used the intact hand for both MI and ME conditions and the phantom limb for the MI condition. Medians and interquartile ranges (IQR) are plotted. Black dots represent the outliers, defined as values more than 1.5 IQR from the nearest quartile. The number of observations for each condition is indicated on the top of each column.

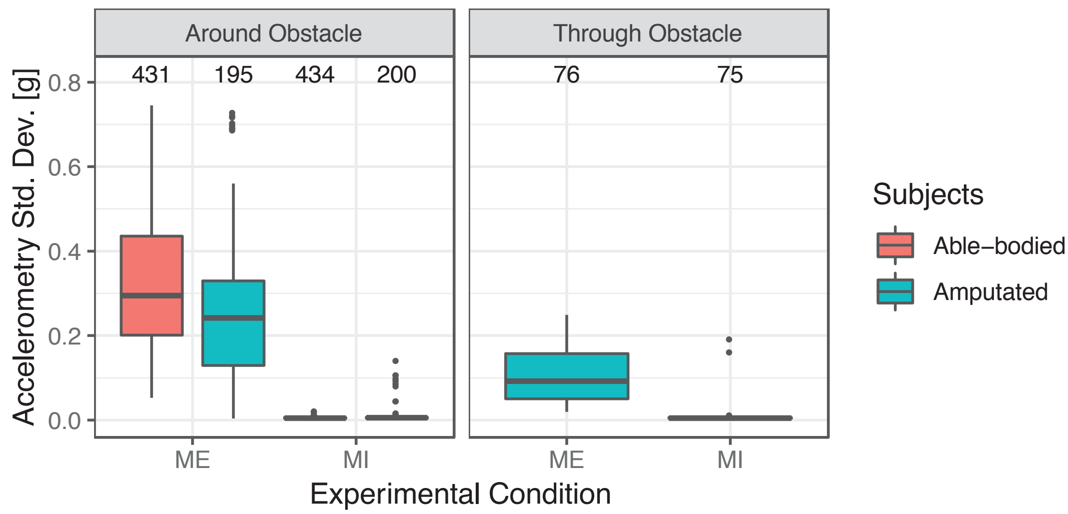

Figure 4. Figure 4. Standard Deviation of the acceleration magnitude of the arm for motor imagery (MI) and motor execution (ME) for exercises 4 and 5. In exercise 4 (left panel) all the participants moved the hands or the phantom around and above the obstacle and exercise 5 (right panel) amputees moved the phantom through the obstacle. Medians and interquartile ranges (IQR) are plotted. Black dots represent the outliers, defined as values more than 1.5 IQR from the nearest quartile. The number of observations for each condition is indicated on the top of each column.

Additionally, we inspected whether the time to completion of the trial in MI and in the ME condition were correlated. The aim was to provide further evidence that in MI, participants were solving the exercise by recruiting a motor strategy. The isochronism between the time to completion of MI and that of ME was previously taken as evidence of the involvement of motor representation in MI (e.g., Parsons, 1994). As illustrated in Figure 5, the correlation between the time to completion of MI and ME was highly significant in exercise 2 in the amputated group for the intact hand (Pearson's correlation coefficient, $r = .72$, $p = 1.309 \times 10^{-10}$) and in the able-bodied control group for the dominant hand (Pearson's correlation coefficient, $r = .59$, $p = 5.461 \times 10^{-15}$). This correlation was also highly significant in exercise 4 (Fig. 6, left panel) for the dominant hand in the able-bodied group (Pearson's correlation coefficient, r

=. 96, p = $5.443*10^{-16}$) and for the intact hand (Pearson's correlation coefficient, r =.90, p = $8.172*10^{-5}$) and the phantom (Pearson's correlation coefficient, r =.93, $3.487*10^{-6}$) in the amputated group. For exercise 5 (Figure 6, right panel), this correlation was also highly significant (Pearson's correlation coefficient, r = .93, p = $9.149*10^{-5}$).

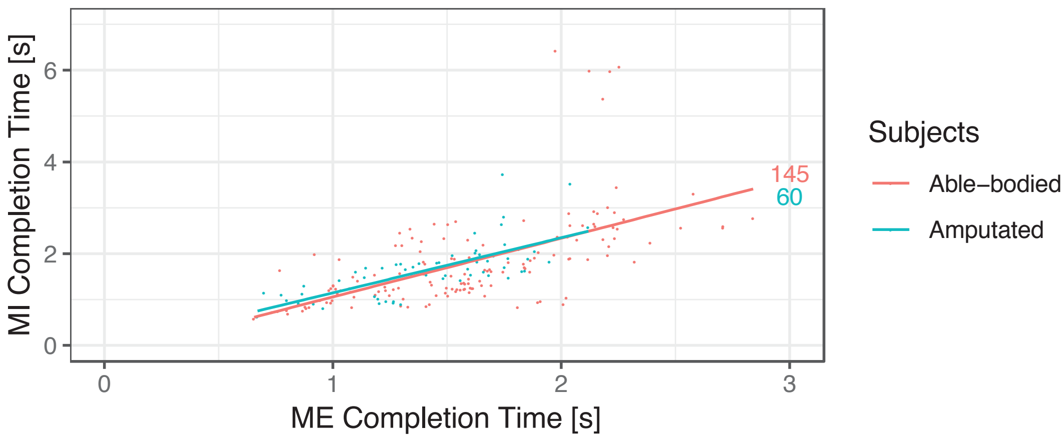

Figure 5. Correlation between the time to completion for motor imagery (MI) and motor execution (ME) conditions in exercise 2 in able-bodied (in red) and amputated (blue) groups. The number of observations for each condition is indicated at the end of each line.

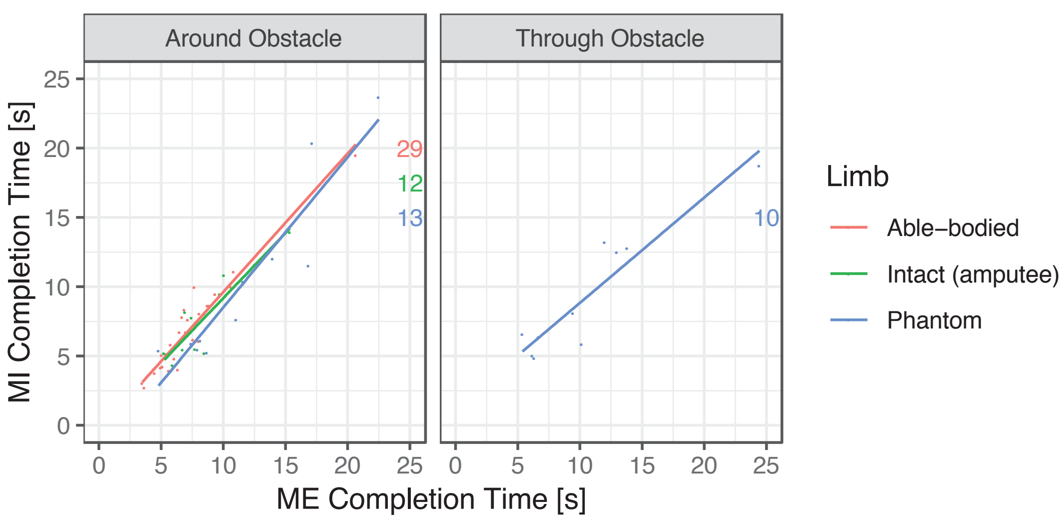

Figure 6. Correlation between time to completion for the motor imagery (MI) and motor

execution (ME) conditions for exercises 4 and 5. In exercise 4 (left panel) all the participants moved the hands or the phantom around and above the obstacle and in exercise 5 (right panel) amputees moved the phantom through the obstacle. The number of observations for each condition is indicated at the end of each line.

MDS2

Assessment of Fitts' Law in Exercise 2

In the able-bodied group, the completion time in both MI and ME was found to decrease with an increasing target width as suggested by previous studies (Sirigu et al., 1996. see Figure 7). Indeed, the influence of the target width on the completion time in both MI and ME was taken as evidence of the involvement of common motor representation in MI and ME (Cerritelli et al., 2000; Decety & Jeannerod, 1995; Sirigu et al., 1996).

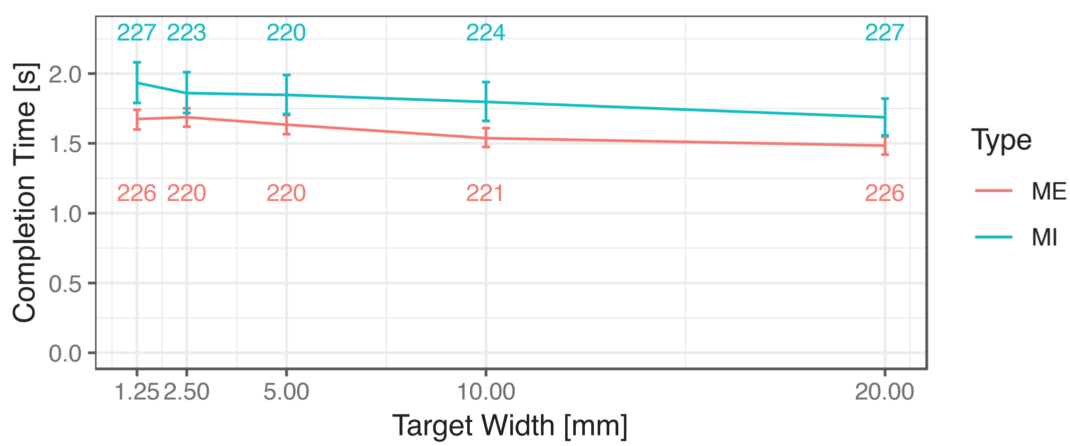

Figure 7. Speed-accuracy trade-off for motor imagery (MI) and motor execution (ME) in exercise 2. The number of observations for each target width is indicated on the top, for MI, and at the bottom, for ME of two lines. Mean and standard error are plotted.

Our data is also compatible with the speed-accuracy trade-off described in previous studies, according to which the difficulty of imagery and real movements is positively related to their time to completion. We further inspected whether these data obey

Fitts' law. According to this law, the index of difficulty can be expressed as a logarithmic function:

$$ID = log_2 \frac{2D}{W}$$

where D is the target distance and W is the target width. Fitts' law states that the completion time (*CT*) presents a linear relationship with the index of difficulty (*ID*), as expressed in the following formula:

$$CT = a + b * ID$$

where *a* (intercept) and *b* (slope) are two coefficients.

In the first two analyses, one for ME and the other for MI, we averaged the time to completion of all the trials by the target width across all the 29 able-bodied participants. For ME, time to completion and index of difficulty were related according to the following positive relationship: $CT = 1.2 + 0.053*ID$, $p = 0.01558$, $R^2 = 0.892$. For MI, the following positive relationship was found: $CT = 1.43 + 0.055*ID$, $p = 0.008598$, $R^2 = 0.9268$. We further explored the linear relationship between the target width and the completion time, which is expressed by this negative relationship for ME ($CT = 1.69 + (-0.011182)*Target\ Width$, $R^2 = 0.915$, $p = 0.01075$) and this other for MI ($CT = 1.92 + (-0.01167)*Target\ Width$, $R^2 = 0.9447$, $p = 0.005619$).

There is a documented modulation of movement history on Fitts' Law (Tang et al., 2018). We thus explored the relationship between *ID* and *CT* and of the target width and *CT* in 8 separate analyses to look at learning effects (corresponding to the 8 trials), considering the *CT* of the n^{th} trial for each target width averaged across the 29 able-bodied individuals. Table 4 summarises the results for ME.

Table 4. Linear relationship between time to completion (CT) and the index of difficulty (ID), and between CT and Target Width for the n trial.

	CT ~ ID				CT ~ Target Width			
Trial n	**a**	**b**	**p value**	**R2**	**a**	**b**	**p value**	**R2**
1	1.35	0.06	0.01	0.93	1.87	-0.01	0.04	0.81
2	1.23	0.06	0.03	0.85	1.71	-0.01	0.06	0.75
3	1.23	0.05	0.01	0.90	1.69	-0.01	0.03	0.85
4	1.20	0.05	0.03	0.85	1.66	-0.01	0.00	0.96
5	1.18	0.06	0.02	0.88	1.67	-0.01	0.01	0.94
6	1.27	0.04	0.10	0.64	1.65	-0.01	0.06	0.74
7	1.14	0.06	0.10	0.64	1.64	-0.01	0.05	0.77
8	1.27	0.04	0.05	0.77	1.58	-0.01	0.01	0.94

The results of our analyses are in line with those of other studies that show an effect of the sequence of trials on Fitts' Law (Tang et al., 2018). Indeed, we observed that when averaging the CT of all the trials irrespective of their sequence of appearance, compared to a nonlinear fit regression, a linear one better predicts the variability in the CT as a function of the target width. However, the opposite is true when considering the first 3 trials separately.

Overall, the data released here confirm the decreasing trend of the function. Furthermore, looking at the participants separately shows high variability in *a* and *b*. In particular, Fitts' law holds for the performance of several subjects with variable *a* and *b* coefficients. High variability of the parameters was reported in literature (MacKenzie, 1995), although the index of performance is usually lower. The discrepancy in the magnitude of these values can be related to the points raised by Guiard & Olasfdottir (Guiard & Olafsdottir, 2011). Other sources of variability of the parameters can be i) the reaching time reflecting the distance between the starting and the target points and ii) the effective dimensions and the relationship between the pointer width and the target width. We hope that our data will contribute to a better understanding of the parameters that constrain presence or absence of Fitts' law, especially in the case of imaginary reaching movements, where precision in reaching the target cannot be measured easily.

USAGE NOTES

Repetitions and Behavioral Data

We invalidated the repetitions in which an error was evident during the acquisition. However, since no feedback on the correct pressing of the footswitch was given to the experimenters, other invalid events might not have been recognized by the examiners. We therefore consider a repetition valid if i) it was not invalidated and ii) if the footswitch was pressed twice, indicating the start and completion of the trial. The total number of trials that was not invalidated manually, as well as the number of repetitions containing invalid behavioral data, are summarized in Table 5. We advise the user to refer to this table when analyzing the data. We suggest the exclusion of the behavioral data of participant 109 due to the high amount of invalid repetitions.

Table 5. Number of invalid repetitions and number of repetitions with invalid behavioral data for all the exercises

		Exercise 2			Exercise 4-5	
	Participant ID	Repetitions	Repetitions with invalid behavioral data		Repetitions	Repetitions with invalid behavioral data
Able-bodied Participants	11	80	7		32	1
	12	80	3		32	0
	13	80	9		32	2
	14	78	4		32	9
	15	80	4		32	5
	16	80	0		32	0
	17	78	0		32	2
	18	80	1		31	2
	19	80	1		32	0
	20	80	0		32	1
	21	80	2		32	1
	22	80	0		32	0
	23	80	0		32	0
	24	80	1		32	0
	26	80	0		32	0
	27	80	1		30	4
	28	80	0		32	3
	29	80	1		32	7
	30	78	6		32	7
	31	80	0		32	0
	32	79	3		32	1
	33	78	4		32	6
	34	80	0		31	2
	35	79	4		32	0
	36	80	7		32	4
	37	80	0		32	0
	38	80	0		32	0
	39	80	8		32	2
	40	79	9		32	0
Transradial Amputees	101	120	20		48	1
	102	120	14		32	5
	103	120	10		32	1
	104	120	16		31	3
	105	109	4		32	1
	106	118	34		40	7
	107	120	5		48	1
	108	120	2		48	0
	109	118	86		48	36
	110	120	5		44	1
	111	120	2		48	0
	112	119	3		47	6
	113	120	2		48	1
	114	n.a.	n.a.		48	0
	115	n.a.	n.a.		31	4

Gaze

Except for the percentage of invalid data, the considerations regarding the gaze data made in Cognolato et al. (2020) are fully valid for this experiment as well. In brief, the acquisition of participants S111 and S114 suffered from a high number of invalid gaze data and a specific physical condition of S115 did not allow the Tobii Pro glasses (Tobii AB, Sweden) to be perfectly stable.

EMG

Even though of limited relevance in this study, unexpected behavior of electrode 1 was noticed for S113. The most affected exercises are exercise 4, exercise 5 and the exercise 2 block executed with the residual limb. However, clipped activations were also noticed in the *imagined* and *motor* parts of exercise 2 for the same participant. The signal characteristics suggested a possible hardware issue ultimately solved by replacing the electrode.

Systematic errors and noise commonly affect accelerometer's data. We estimated the calibration parameters for the accelerometers embedded in the Delsys Trignlo electrodes and for the IMU of the Tobii glasses (Tobii AB, Sweden) according to the method described in Tedaldi et al. (2014). The calibration parameters and the original data are included in the *accelerometer_calibration.tgz* archive within the MDSScript dataset (Gijsberts, 2019).

MDS2

Participant S013 was erroneously asked to perform exercise 2 with his non-dominant (right) hand. All other able-bodied participants performed the exercise with their dominant hand; hence, this participant's data may not be entirely comparable to the population data.

Participant S115 did not participate in exercise 2. Furthermore, participant S114 who had both hands amputated, performed the exercise using the phantom right hand.

MDS4

In some acquisitions, the obstacle was placed vertically on its smallest face, resulting in a height of 31.7 cm instead of 26 cm. When incorrectly positioned, the position of the box was kept identical for all conditions of exercises 4 and 5. The different positioning, associated with a height of 31.7 cm, occurred in many participants, indicated with the label “high” in Table 6.

Table 6. High or Low position of the obstacle in exercise 4 during each participant's data acquisition. High: the obstacle was placed vertically on its smallest face in the height of 31.7 cm, low: this height was 26 cm.

EX4			
BOX POSITION			
Amputees		Able-bodied	
S101	low	S011	high
S102	low	S012	high
S103	high	S013	high
S104	low	S014	low
S105	low	S015	low
S106	high	S016	high
S107	high	S017	low
S108	low	S018	low
S109	low	S019	low
S110	low	S020	low
S111	high	S021	high
S112	low	S022	low
S113	low	S023	low
S114	low	S024	low
S115	low	S026	high
		S027	low
		S028	low
		S029	low
		S030	low
		S031	low
		S032	low
		S033	high
		S034	low
		S035	high
		S036	low
		S037	low
		S038	low
		S039	low
		S040	low

MDSInfo

Data on qualitative and quantitative aspects of PLS are generally available for all participants with only very few missing data points as indicated in Table 7.

Table 7. Overview of the missing neurocognitive tests.

ID	Missing Tests	Motivation
111	VMIQ-2, DASH, Body Representation in dreams	Language Barrer
105	VMIQ-2	Time pressure
106	VMIQ-2	Participant's wish to discontinue the experiment

S109

Participant S109 presented a considerable number of invalid behavioral trials for all the exercises that could be explained by several factors. We suggest that the participant might not have paid attention to correctly press the pedal at the beginning and the end of the trials. We, therefore, discourage the use of participant's S109's behavioral data.

Code Availability

The repository MeganePro Script Dataset (Gijsberts, 2019) also hosts the MATLAB (version 2016b, MathWorks, Natick, MA, USA) code used for the post-processing procedure and the validation scripts used to obtain the results reported in this manuscript. The README file contained in the *megane_postprocess.tgz* archive describes and reports the scripts used for the data processing. The code used for the technical validation included in this paper and to produce the corresponding figures are within the *meganepro_validation_ex245.tgz* archive. These scripts are commented in a step-by-step manner, and they can be inspected and run using R studio (Version 1.1.442). The file *ex2_validation.R* contains the code used for the technical validation of exercise 2, while the file *ex4_validation.R* was used for technical validation of exercises 4-5.

The original data cannot be released to ensure the privacy of the participants. However, the provided code contains all the steps taken during each stage of the data processing and technical validation. Furthermore, they can be adapted and applied to similar tasks and similar validation/statistical questions by the interested researchers.

STUDY 5. PHANTOM LIMB SENSATION II

Apparent motion perception in lower limb amputees with phantom sensations: “Obstacle Shunning” and “Obstacle Tolerance

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Author contributions: GS wrote the manuscript and performed data analyses. IG, AT collected the data. MG, PB, BL ideated and designed the acquisition protocol.

ABSTRACT

Phantom limbs are the phenomenal persistence of postural and sensorimotor features of an amputated limb. Although immaterial, their characteristics can be modulated by the presence of physical matter. For instance, the phantom may disappear when its phenomenal space is invaded by objects ("obstacle shunning"). Alternatively, "obstacle tolerance" occurs when the phantom is not limited by the law of impenetrability and co-exists with physical objects. Here we examined the link between this under-investigated aspect of phantom limbs and apparent motion perception. The illusion of apparent motion of human limbs involves the perception that a limb moves through or around an object, depending on stimulus onset asynchrony (SOA) for the two images. Participants included 12 unilateral lower limb amputees matched for obstacle shunning (n=6) and obstacle tolerance (n =6) experiences, and 14 non-amputees. Using multilevel linear models, we replicated robust biases for short perceived trajectories for fast SOA (moving through the object), and long trajectories (circumventing the object) for slow SOAs in both groups. Importantly, however, amputees with obstacle shunning perceived leg stimuli to predominantly move through the object, whereas amputees with obstacle tolerance perceived leg stimuli to predominantly move around the object. That is, in people who experience obstacle shunning, apparent motion perception of lower limbs is not constrained to the laws of impenetrability (as the phantom disappears), and legs can therefore move through physical objects. Amputees who experience obstacle tolerance, however, have stronger solidarity constraints for lower limb apparent motion, perhaps because they must avoid co-location of the phantom with physical objects. Phantom limb experience does, therefore, appear to be modulated by intuitive physics, but not in the same way for everyone. This may have important implications

for limb experience post-amputation (e.g., improving prosthesis embodiment when limb representation is constrained by the same limits as an intact limb).

INTRODUCTION

Body representation defines a crucial component of self-awareness that results from integrated activity of both bottom-up and top-down neural mechanisms operating at multiple levels of processing (Azanon et al., 2016). The emergent product of such mechanisms is the complex experience that my own body *belongs to me*, and that its single segments have a precise length, and occupy a well-defined position in space (Lopez, Halje, & Blanke, 2008). Importantly, the self is normally localized within the borders of the body (Arzy et al., 2006; Lenggenhager et al., 2007), but can be experienced as functionally extending beyond the body (e.g., during tool use; Maravita & Iriki, 2004). Moreover, "embodiment" of physical objects and substitute body parts (e.g., rubber limbs, or a prosthetic limb) can significantly alter the experience of the bodily self (Giummarra et al., 2008).

After dramatic changes to the physical body due to amputation, almost all amputees experience the presence of a phantom limb at least occasionally (Ramachandran & Hirstein, 1998). In the case of phantom limb sensations, the general law that the anatomical borders of the body constrain the extension of the self no longer applies. Instead, phantom limbs reflect the preserved neural representation of the body (Makin et al., 2013), and are typically perceived to be localized in extra-corporeal space, as a veritable "out-of-limb" experience. An important issue that needs clarification is whether extension of the spatial limits of the self during tool use may be functionally similar to embodiment of a prosthetic limb (Giummarra et al., 2010). While prosthetic limbs may be functionally equivalent to a tool (van den Heiligenberg, et al., 2017), albeit as a limb substitute rather than a limb extension, clinicians pose divergent views regarding the interaction between the phantom limb and prosthesis. Some argue that vivid phantom limb awareness positively influences dexterous use of a functional prosthesis; however, others note that the phantom limb may interfere with proper embodiment of the prosthesis (e.g., Mayer et al., 2008).

The phenomenon of "obstacle shunning", rarely assessed in clinical contexts and never examined to date in cognitive science, may offer unique insight into changes in body and object representation after amputation, and the interaction between a phantom limb and extracorporeal objects, such as a prosthesis. During obstacle shunning the amputee reports that their phantom limb moves aside, telescopes or fades from awareness once its phenomenal and visually accessible space is occupied by a solid object (Jalavisto, 1950). Whether or not the phantom limb disappears when its space is violated may provide significant insights into the mechanisms underlying bodily awareness, and the contribution of visual perception in body experience.

Shunning behavior illustrates the visual capture of body awareness. Here, the mere visual analysis of an object's characteristics and its location in space can modulate the multisensory (proprioceptive, postural and motor) integration that underpins the awareness of a phantom in space. Conversely, in the case of "obstacle tolerance" where the phenomenal space of a phantom, by definition, overlaps with the space occupied by an object, the visual contributions to bodily awareness may be reduced.

There is a wealth of clinical observations on the phenomenon of obstacle shunning in amputees. Abbatucci's (1984) famous "choc-a-blanc" (i.e. the sudden stroke, with a ruler, to the space an individual patient localizes his or her phantom), was used to classify amputees according to their reaction. These reactions varied from complete indifference to a state of being most painfully touched. Likewise, others have emphasized that the observed variability in obstacle shunning belongs to the most evident individual differences in the perception of phantom limbs (Henderson & Smyth, 1948; Katz, 1920; Poeck, 1964). In fact, about 50% of amputees can move their phantom through solid objects without notable changes in its phenomenal appearance (Haber, 1956; Jalavisto, 1950). Obstacle shunning appears to be a behavioral reaction that is guided by "intuitive physics", specifically regarding fundamental knowledge about the mutual impenetrability of two solid objects (see Heinemann, 1945, for the philosophical dimension). Presumably, those who report obstacle shunning consider their phantom limb realistic enough to adhere to this law of impenetrability. On the contrary, those who do not experience obstacle shunning may conceptualize their phantom body part, despite its perceptual vividness, as a mere "sensory ghost" (Mitchell, 1866), and may consciously or subconsciously disregard these basic physical laws. The visual capture of body awareness might rely upon the nature of the object. For instance the presence of inanimate physical objects may well lead to a shunning behavior which differs from that induced by human body parts (see Brugger, 2006). And even among inanimate objects, it remains to be examined whether shunning or tolerance behaviors are affected by the valence of the object (e.g. neutral vs threatening objects).

Individual differences in obstacle shunning, which are so broadly described in the clinical literature, have not yet received the attention they deserve in modern empirical studies of phantom limb experience. Here we set out to re-introduce the topic in an experimental study of corporeal awareness as modulated by high-level cognitive factors. We borrowed an experimental paradigm from the cognitive science of motion perception, which we now describe.

In a pioneering study, Shiffrar and Freyd (1990) presented able-bodied observers with pairs of photographs depicting human bodies. The second picture of each pair differed from the first only in a minor alteration with respect to the position of one body part. In the second picture, the body part was always hidden by either another body part, or by a solid object, whereas in the first picture the "active" body part was in the foreground. When flashed in a defined succession, participants reported perceiving illusory limb movements, and the motion path critically depended on the speed at which they alternated (i.e., stimulus-onset-asynchrony, SOA). Short SOAs tended to elicit the perception of the shortest, biologically impossible path whereby the body part seemed to have moved right *through* the object or body part. In other words, the visual perception violated the law of impenetrability of two solid objects. In contrast long SOAs (>400 ms) brought about the perception of "visual obstacle shunning" whereby the body part was perceived to have moved along a physically plausible trajectory *around* the object or stationary body part. The interpretation of these effects was that the central nervous system requires sufficient time to allow top-down processes to influence perception. When sufficient time is available, implicit knowledge about the impenetrability of solid objects modifies the trajectory of apparent motion perception in order to avoid violation of basic physical rules. Shiffrar and Freyd (1990) proposed the term "solidity constraint" to describe this top-down influence.

The effects of SOA on apparent motion perception have been replicated in several follow-up studies in able-bodied persons (Stevens et al., 2000), amputees (Moseley & Brugger, 2009), and in persons born without limbs (Funk, Shiffrar, & Brugger, 2005; Vannuscorps & Caramazza, 2016). For instance, Stevens et al. (2000) showed that the shift between perception of a plausible and non-plausible movement trajectory is marked, at a neurofunctional level, by distinct patterns and networks of neural activity. Specifically, perception of a *plausible* movement trajectory, but not an *implausible* movement, was associated with the selective activation of fronto-parietal areas typically involved in sensory-motor integration and the maintenance of internal body representations (Wolpert, Goodbody, & Husain, 1998). These findings support the motor hypothesis whereby *visual* illusory perception of limb movements might depend on somatosensory and motor representations of an observer's own corresponding limb, acquired by means of motor execution (Knoblich, 2008; Thornton, 1998). Furthermore, they are in line with the results of a more recent study from where seven arm amputees with phantom limb sensation reported their perceptions in an apparent motion task before and after a training to execute biologically impossible movements of the phantom at the wrist. Before training they performed similarly to non-amputees with SOA-dependent perceptions of apparent motion. After completing the training, however, the amputees were more likely to perceive the biologically impossible motion trajectory regardless of the SOA between the two static pictures. These effects occurred when the depicted limb in the trials were consistent with the side of amputation, but not for the contralateral limb. More recently, Vannuscorp & Caramazza (2016) investigated differences in the illusory motion perception of upper limbs rotating according to biomechanically possible or impossible path in five participants with bilateral upper limb dysplasia who presented with somatosensory alterations, compared with able-bodied and normally developed participants. They found no between groups differences concerning the SOA effect, concluding that apparent motion perception might rely on visual information encoded at the level of an observer's visual system. However, their paradigm did not consider the specific interaction of a human body part or a phantom limb with external objects. The paradigm of apparent motion of body parts has thus, to the best of our knowledge, never been investigated in relation to everyday experience of solidity constraints by a phantom limb.

In this study, we investigated apparent motion perception in leg amputees and non-amputee controls and examined whether illusions varied in relation to whether or not amputee participants experience obstacle shunning with their phantom limb during everyday life. Adding another neglected issue to the current state of the literature on apparent motion perception, i.e. the valence of an object in the trajectory of perceived limb motion, we included stimuli depicting arms or legs, and solid objects that were either neutral (e.g. a broom handle) or "threatening" (e.g., fire). As a main hypothesis, and in elaboration of a previous speculation on differences "*in those subjects who report shunning behavior in their spontaneous phantom experiences*" (p. 195) (Brugger, 2006), we here based our predictions on some basic tenets of intuitive physics. That is, the empirical evidence that two objects cannot take the same place at once (the "law of impenetrability"). Therefore, we expected that lower limb amputees who experience obstacle shunning would predominantly perceive legs to move through objects as their phantom ordinarily disappears from awareness when a solid object occupies its phenomenological space. In contrast, we speculate that obstacle tolerance arises due to a more rigid representation of the phantom, which would thereby impose the same solidity constraints as a normal limb. Thus, amputees who experience obstacle tolerance were expected to perceive leg stimuli to predominantly move around objects. Furthermore, we explored whether apparent motion might be modulated by the valance of the seen physical stimulus.

METHODS

Participants

Twenty-six participants with no neurological or psychiatric disorders volunteered, including 12 lower limb amputees (11 male; *m* = 52.17 years old; *sd* = 9.67) and 14 non-amputees (10 male; *m* = 36.00 years old; *sd* = 10.01). A Mann Whitney U test showed that that age was significantly different between the amputee and non-amputee groups ($p < 0.05$).

There were six amputee participants who experienced obstacle shunning (6 male; *m* = 55.0, *sd* = 7.54) and six who experienced obstacle tolerance (5 male, *m* = 49.33, *sd* = 11.39). Nine participants had below-knee amputations, and three had above-knee amputations. Participants were recruited from the Caulfield Hospital amputee unit, the Limbs4Life support group, and Monash University in Australia. Volunteers provided informed consent in line with the Helsinki Declaration (1964). The study was approved by the Human Research Ethics Committee of Alfred Health, and the experiment was conducted at Monash University. Amputees were only eligible if they had a unilateral lower limb amputation, and experienced phantom limb sensations (painful or painless) in everyday life, as assessed by a battery of baseline questionnaires.

Materials and procedures

All participants provided demographic information, and amputee participants completed questionnaires about pain, disability, and phantom limb experience.

The *Brief Pain Inventory* (BPI) measured pain intensity and pain-related disability (Cleeland, 1989). Participants answered questions of "How intense is your phantom pain right now?" and "How intense was your phantom limb pain on average during the last 6 months?" on an 11-point Likert scale (0 = *no pain*; 10 = *worst pain I can imagine*). Tan et al. (2004) showed a high reliability and validity of the BPI for persons suffering from non-malignant chronic pain.

Short-Form McGill Pain Questionnaire (SF-MPQ; Melzack, 1987) measured the sensory and affective qualities of phantom limb pain. The SF-MPQ comprises 15 pain descriptions covering both sensory ($n = 11$) and affective ($n = 4$) categories of the standard MPQ. Wright, Asmundson, and McCreary (2001) confirmed the validity of this two-factor model of pain.

Phantom limb experience. Amputee participants provided information about their phantom limb sensations and pain. Participants reported the intensity, duration and frequency of phantom pain, whether the phantom felt like it was a part of their body, and whether they could move the phantom limb. They indicated whether emotional (e.g., anger, sadness, fear, happiness, stress, and relaxation), biological or sensory states (e.g., micturition, defecation, combing, shaving, observing an amputee, and observing another person in pain) influenced their phantom pain. Amputee participants were asked whether their phantom limb disappears when it comes in contact with a physical object, with possible answers of never, sometimes or always. Participants were classified into an Obstacle Tolerance group (n = 6; never disappears) and Obstacle Shunning group (n = 6; sometimes disappears).

Stimuli

In the experimental task pairs of images were presented in sequence with each stimulus pair comprising one picture with the target limb in front of a solid object and another with the limb behind the same object (See Figure 1a). There was a total of 32 stimulus pairs featuring arms (n = 16) or legs (n = 16) and threatening (n = 16) or neutral (n = 16) objects. Each stimulus depicted apparent motion for the left limb, which was then duplicated and inverted to provide right limb stimuli. Two stimulus pairs depicted apparent motion of one arm or leg through the other arm or leg, respectively, with the latter limb remaining in a fixed position in both images. The final stimulus set also comprised a 50:50 ratio of male and female models. Attempts were made to ensure that objects in each category were balanced with respect to visual features of shape and size so that the primary source of variance was attributable to valence (see supplementary Tables 1 & 2 for an overview of the stimuli). A pilot of the a larger set of stimuli in a separate sample of five healthy volunteers revealed that the 32 stimuli were most appropriate for inclusion based on ratings of the nature of the stimulus object on an 11-point scale (0 = pleasant object, 5 = neutral object, 10 = threatening object). Moreover, using the Self-Assessment Manikin (Lang & Bradley, 2007) rating system, participants rated the valence ("how does this picture make you feel"; 1 = happy to 9 = unhappy) and arousal ("how does this picture make you feel"; 1 = excited to 9 = calm) of the stimuli. Participants in the study completed the same ratings, which confirmed that the pictures elicited the desired emotional states in the study sample.

Experimental task

The apparent motion experimental task was programmed using the software SuperLab 4.5 Cedrus (San Pedro, California). Each stimulus pair was presented alternately with varying stimulus duration (SD) and inter-stimulus-interval (ISI) at either long or short SOA. The long SOA had a presentation rate of 1.3 Hz (SOA = 750ms; SD = 400ms; ISI = 350ms), and the short SOA had a presentation rate of 4 Hz (SOA = 250ms; SD = 150ms; ISI = 100ms). In every trial, participants were presented with a blank screen with a central fixation cross (1 second) followed by a stimulus pair that was presented three times to create a flickering dynamic image sequence, resulting in trials of 4.50s (long SOA) and 1.40s (short SOA) duration. After each trial participants provided a binary response indicating, by key press, whether they perceived the most direct *short* movement of the body part (i.e., through the solid object, coded as -1, Figure 1b), or the indirect *long* pathway (i.e., around the solid object, coded as +1, Figure 1c).

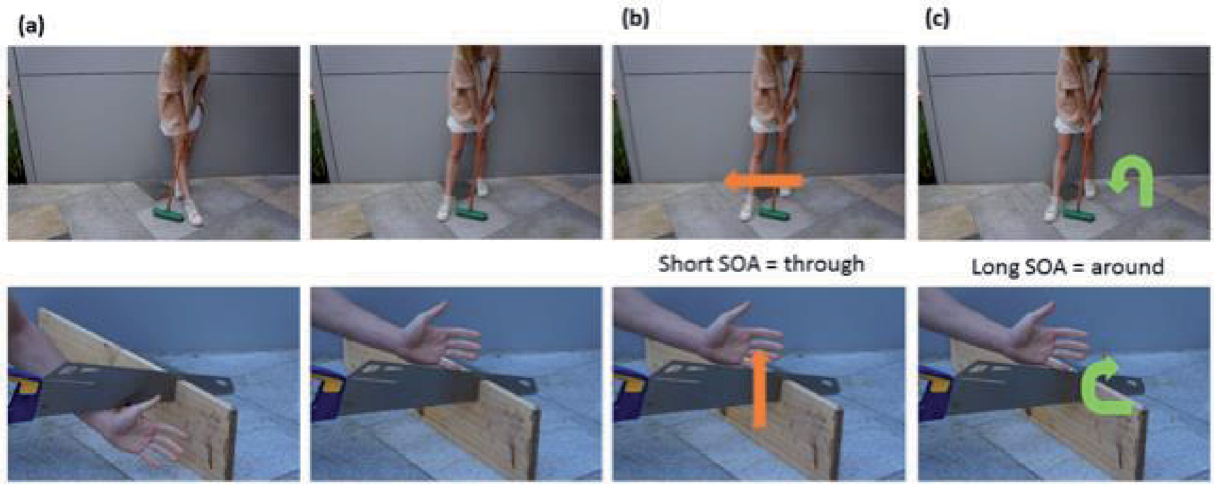


Figure 1. Experimental set up, with (a) an example neutral (i.e., broom) and threatening (i.e., saw) where the limb is on one side of the stimulus in the first image and on the opposite side in the second; and the two possible pathways of apparent motion either (b) direct biologically impossible pathway typically reported during fast SOA, or (c) the indirect and biological possible pathway typically reported during slow SOA.

There were 32 blocks, each comprising five trials, which controlled for within subjects conditions of SOA (16 short SOA blocks; 16 long SOA blocks), valence (16 threatening blocks; 16 neutral blocks), limb laterality (16 left limb blocks; 16 right limb blocks) and limb (16 arm blocks; 16 leg blocks). The blocks were presented in a pseudo-randomized order. At the end of each block, amputee participants rated the intensity of their phantom pain at that moment on an 11-point Likert scale (0 = *no pain*; 10 = *worst imaginable pain*). At the end of the full apparent motion task, participants rated the valence, arousal, and threatening nature of each stimulus object using the same rating scales that were used in an initial pilot of the experimental paradigm, described under the stimulus properties above.

Data analysis

Data were analyzed with R studio Version 1.0.136. Data were manually checked for assumptions of ANOVA and linear mixed model analyses, which were fitted with the R *lme4* package (Bates et al., 2015). Specifically, inconsistent data and outliers were screened using Z-scores (i.e., detecting those > 2 SD from 0), and with boxplots and stem-and-leaf displays. For both the ANOVA and linear mixed models independence of the residuals, and normal distributions were examined through inspection of histograms and Q-Q Plot. The Shapiro-Wilk test showed that both standardized and unstandardized residuals were normally distributed for all data ($p > 0.05$). There were no missing data. Alpha was set at <0.05, or 95% confidence intervals (CIs) that do not include zero, for significant effects, and Bonferroni adjustments were applied to post-hoc tests.

Valence and arousal ratings for stimuli in the threatening and the neutral blocks were examined using Cronbach's alpha (internal consistency), inter-item correlations, and descriptive statistics were reported to confirm that stimuli were perceived as threatening or not in accordance with their allocation. Within-subjects ANOVA examined whether valence ratings were significantly different between neutral and threatening stimuli.

Given that amputee participants must experience phantom limb sensations, and vary in their experience of obstacle tolerance or shunning in everyday life, the sample was constrained by the size of the potential patient population. To examine the study hypotheses we considered each behavioral data point (there were more than 4000 across all participants), while adjusting for within-subject and within-group dependence using multilevel modelling. This ensured that the analyses were as rigorous, robust and adequately powered as possible despite the small sample in the amputee and non-amputee groups.

The outcome measure, the illusion experience, was the tendency to report that the limb moved around the object (coded as +1) or that the limb moved through the object (coded as -1). The response was therefore quantified as the percentage of reporting +1 and -1 across trials, and could range between -1 and +1. Significant findings were visualised using pirate plots, which were generated in R through the package "yarrr" (Phillips, 2017). Pirate plots demonstrate the mean (95% CI) value and spread of ratings between +1 (apparent motion around the object) and -1 (apparent motion through the object). This style of visualization also demonstrates whether the frequency of illusion experiences differ significantly from a 50:50 ratio (i.e. the value of 0 lays within the confidence interval).

Sensitivity analyses

Linear mixed models were used given the longitudinal structure of the data, and within person dependence (Fox, 2002). Models first examined illusion experience in amputees and controls separately (see supplementary results) before conducting hypothesis testing. These showed that missing limb laterality (amputees only) and stimulus laterality (amputees and controls) did not predict illusion experience, nor did they improve model fit when examining the change in -2 log-likelihood (Bliese & Ployhart, 2002), and these factors did not need to be included as fixed factors in the primary hypothesis testing models. Stimulus valence, SOA and limb were significant predictors of illusion in amputees and controls, and were therefore included in the hypothesis testing models.

Hypothesis testing

Linear mixed models were used to examine apparent motion illusion experience between subjects (amputees / non-amputees) in relation to stimulus valence (threatening / neutral), SOA (short / long) and limb (leg / arm). Several models were fit in a step-wise manner in line with the study hypothesis. The final model included fixed effects of group and stimulus valence, SOA, limb, two-way and three-way interactions between each of these factors, and a random intercept for participant ID given the random structure of the data ($ICC(1) = 0.23$, $F(11, 1908) = 47.48$, $p < 0.0001$). The analyses applied the methods proposed in Field (2009), and showed that slopes for the group factor did not vary across participants ($\chi^2(2) = 0.02$, $p = 0.99$).

Furthermore, adding the factor age as fixed factor, accounting for the between group difference in age, has not improved the fit of the model ($\chi^2(1) = 1.37$, $p = 0.24$) suggesting that this factor might have only a limited impact on the performance of the participants.

Linear mixed model analyses were then used to examine illusion experience within amputees to identify differences in the amputee groups (Obstacle Tolerance group / Obstacle Shunning group). First fixed effects of amputee group and stimulus valence, SOA and limb, and the two-way and three-way interactions between each factor. A random intercept for participant was modelled ($ICC(1) = 0.22$, $F(11, 1908) = 46.41$, $p. < 0.0001$). A random slope for the factor group was initially modelled but then omitted as it did not improve model fit when evaluating the change in -2 log-likelihood ($\chi^2(2) = 0.28$, $p = 0.87$). Furthermore ,adding the factor age as a fixed factor did not improve the fit on the model ($\chi2(1) = 0.05$, $p = 0.82$). For all models, Tukey post-hoc tests were undertaken, after checking the homogeneity of the variance, to examine any significant interactions, and Bonferroni corrections were applied to correct for multiple post-hoc analyses. Moreover, one-sample t-tests examined whether perceptual biases differed significantly from zero, whereby zero would indicate a 50:50 ratio of perceiving the limb to move through and around the object.

RESULTS

Amputee characteristics

The amputee participant characteristics are summarised in Table 1. The two amputee subgroups did not differ in the number of years since amputation (obstacle shunning group: $n = 6$; *Med* = 5.5 years since amputation, *range*: 1 to 36 years; obstacle tolerance group: $n = 6$; *Med* = 5.5 years since amputation, *range*: 1 to 10 years, $p = 0.94$).

Table 1.Overview of the amputation and phantom limb experience characteristics for each amputee participant.

Amputation			Phantom sensations and pain							
Level (side)	Time since (years)	Cause	Is the phantom "part of" your body?	Is the phantom pleasant?	Can you move the phantom?	Duration of PLP [a]	Usual PLP Intensity	PLP Intensity Right now	Emotion impact on PLP	Shunning Experience [a]
Below knee (R)	15	Trauma	yes	no	no	6	7	7	Yes (stress, relaxation)	Yes
Below knee (R)	4	Diabetes	no	yes	no	1	3	0	No	Yes
Below knee (L)	<1	Vascular disease	yes	no	yes	3	8	0	No	Yes
Below knee (R)	36	Trauma	no	no	yes	7	5	2	No	Yes
Below knee (L)	1	Diabetes	no	no	yes	7	8	1	No	Yes
Above knee (L)	7	Trauma	yes	yes	yes	8	5	3	Yes (anger, sadness, stress, relaxation)	Yes
Below knee (L)	9	Trauma	yes	yes	yes	10	9	4	No	No
Below knee (R)	11	Trauma	yes	no	yes	3	1	0	No	No
Above knee (R)	6	Infection	yes	no	yes	5	3	1	No	No
Below knee (R)	10	Cancer	no	no	no	6	3	2	Yes (anger, sadness)	No
Below knee (L)	3	Osteomyelitis	yes	yes	yes	3	6	0	Yes (anger, sadness)	No
Above knee (R)	5	Cancer	yes	yes	no	1	1	1	Yes (Stress)	No

Notes: [a] 1 = seconds, 10 = continuous; [b] All participants who reported that the phantom disappeared (i.e., "obstacle sunning") reported that it happened "sometimes". *Abbreviations*: PLP = phantom limb pain.

Stimulus ratings

The threatening stimuli (*m* = 5.76, *sd* = 1.37; Cronbach's *a* = 0.96) were consistently rated as more unpleasant than the neutral stimuli (*m* = 4.66, *sd* = 1.14; Cronbach's *a* = 0.94), $F(1,25) = 20.34$, $p < 0.001$, $\eta^2 = 0.45$. Likewise, the threatening stimuli (*m* = 5.41, *sd* = 1.74; Cronbach's *a* = 0.97) were rated as more arousing (note: lower scores indicate higher arousal) than the neutral stimuli (*m* = 6.24, *sd* = 1.57; Cronbach's *a* = 0.96), $F(1,25) = 8.48$, $p = .007$, $\eta^2 = 0.25$.

Apparent motion illusion in amputee and control participants

Linear mixed model analysis examined potential differences between groups (amputee/ non-amputee) in illusion perception with respect to SOA (short/ long), stimulus valence (threatening/ neutral), and stimulus limb (arm/ leg). All fixed effects are reported in Supplementary Table 5, and the Tukey contrasts are reported in Supplementary Table 6. This analysis replicated, in amputee and non-amputee participants together, the well-known effect of the SOA (*b* = -0.40, 95% CI: -0.53,-0.26, $t(4121) = -5.83$, $p < 0.001$, odd ratio: 0.69), whereby the limb appeared to move through the object in trials with short SOA (*m* = -0.21, *SE* = 0.02) and around the object in trials with long SOA (*m* = 0.07, *SE* = 0.02), and these perceptual biases differed significantly from zero (short SOA: $t(2{,}079) = -9.73$ $p < 0.001$; long SOA: $t(2{,}079) = 3.34$, $p < 0.001$).

There was no effect of group ($p = 0.98$), but there was a two-way interaction between group and stimulus limb (*b* = 0.24, 95% CI = 0.057 to 0.42, $t(4121) = 2.58$, $p < 0.01$). Tukey post-hoc tests showed that this interaction effect was only attributable to a difference in perceptual biases for the amputee group between trials depicting arms and legs (*Mdiff* = 0.12, *SE = 0.04,* $p = 0.026$ Bonferroni corrected), and t-tests showed that there was only a significant bias (i.e., significantly different to zero) for arm trials ($t(959) = -2.069$, $p = 0.038$), such that arms were perceived to move through objects, and no significant apparent motion bias in trials comprising legs for amputee participants ($t(959) = 1.49$, $p = 0.14$). Tukey post-hoc tests revealed no differences in apparent motion illusion between leg and arm trials in the control group ($p = .13$). Rather both arms ($t(1,119) = -5.45$, $p < 0.001$) and legs ($t(1,119) = -2.52$, $p = 0.012$) were perceived to move through the object for non-amputees.

There were two-way interactions between group and limb ($b = 0.24$, 95% CI: 0.06 to 0.42, $t(4,121) = 2.58$, $p = 0.01$), and valence and limb ($b = -0.34$, 95% CI: -0.51 to -0.16, $t(4,121) = -3.79$, $p < 0.001$), and a three way interaction between group, valence and limb ($b = -0.22$, 95% CI: -0.42 to -0.009, $t(4,121) = -2.038$, $p = 0.042$), see Figure 2. Tukey post-hoc tests showed that the strongest specific effects in these interactions were attributable to differences in perceptual biases, for both groups, between (a) arm and leg trials (amputees: $Mdiff = -0.38$, $SE = 0.056$, $p < 0.001$; controls: $Mdiff = -0.25$, $SE = 0.052$, $p < 0.001$, both Bonferroni corrected); and (b) neutral and threatening leg trials (amputees: $Mdiff = 0.55$, $SE = 0.056$, $p < 0.001$; controls: $Mdiff = 0.41$, $SE = 0.052$, $p < 0.001$, both Bonferroni corrected). T-tests then confirmed that the perceptual biases differed significantly from zero for neutral leg trials (amputee: $t(479) = 7.52$, $p < 0.001$; control: $t(559) = 3.15$, $p = 0.002$), which appeared to move around the object, and threatening leg trials (amputee: $t(479) = -5.15$, $p < 0.001$; control: $t(559) = -6.95$, $p < 0.001$), which appeared to move through the object. While the control group perceived arms to move through the object regardless of valence (neutral: $t(559) = -2.75$, $p = 0.007$; threatening: $t(559) = -5.01$, $p < 0.001$), amputee participants did not perceive a bias towards either motion path for neutral ($p = 0.20$) and threatening ($p = 0.10$) arm stimuli.

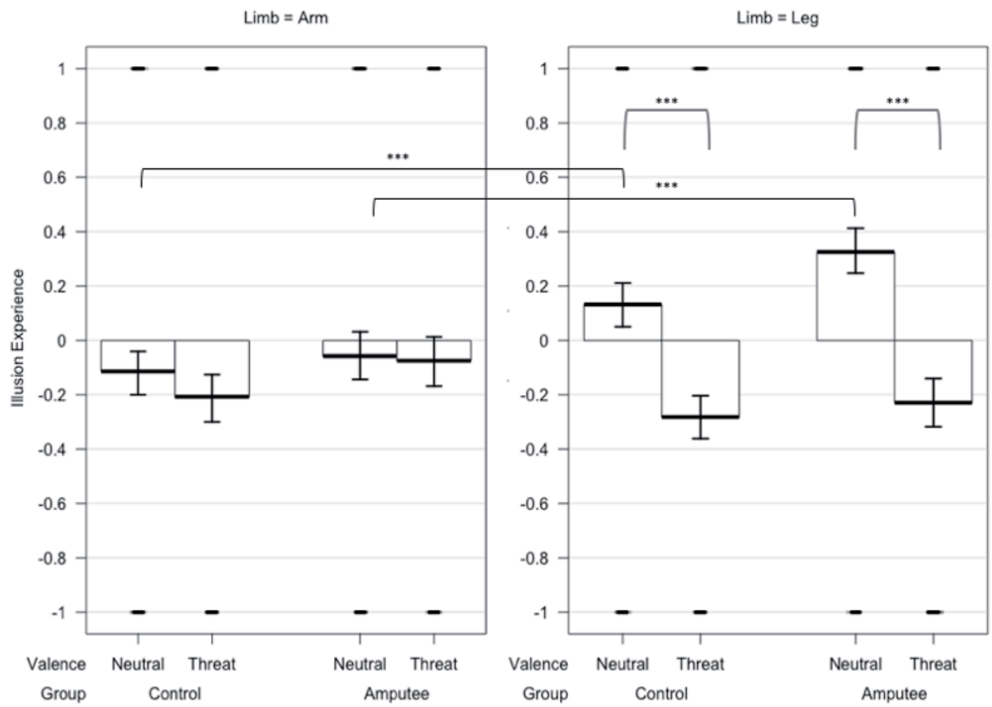


Figure 2 Apparent motion illusion experience between groups (amputee vs non-amputee) in relation to limb (arm / leg) and valence (neutral / threatening).

Obstacle shunning group and obstacle tolerance group

Differences in apparent motion illusions between the Obstacle Tolerance group and Obstacle Shunning group were examined using a linear mixed model with fixed effects for SOA (long/ short), stimulus valence (threat/ neutral), and stimulus limb (arm/leg), and all the fixed effects are reported in Supplementary Table 7. Consistent with the findings reported above in amputee and non-amputee participants together, there were significant effects of SOA (b = -0.32, t(1895) = -3.18, 95% CI = -0.52 to -0.13, p < 0.001), stimulus limb (b = 0.63, t(1,895) = 6.18, 95% CI = 0.43 to 0.83, p < 0.001) and interaction between valence and limb (b = -0.49, t(1,895) = -3.67, 95% CI = -0.75

to -0.23, $p < 0.001$) on apparent motion experience. There was no main effect of group ($p = 0.31$), or interaction between group and SOA ($p = 0.27$).

There was an interaction between group and stimulus limb ($b = -0.35$, $t(1,895) = 2.67$, 95% CI = -0.61 to -0.094, $p < 0.008$), see Figure 3a. Tukey post-hoc tests confirmed that both amputee subgroups experienced different illusions between leg and arm stimuli (obstacle tolerance group: *Mdiff* = 0.39, *SE* = 0.06, $p < 0.001$; *Mdiff* = -0.16, *SE* = 0.057, $p = 0.032$, both Bonferroni corrected); however, the direction of the perceptual biases differed in each group. T-tests confirmed that for the obstacle tolerance group leg stimuli appeared to move around the object ($t(479) = 4.37$, $p < 0.0001$), and arm stimuli appeared to move through the object ($t(479) = -4.27$, $p < 0.0001$) with both biases differing significantly from zero. On the contrary, for the obstacle shunning group, leg stimuli appeared to move through the object ($t(479) = -2.20$, $p = 0.028$), but the illusion for arm stimuli did not significantly differ from zero ($p = 0.20$).

There was an interaction between group and stimulus valence ($b = -0.29$, $t(1,895) = -2.16$, 95% CI: -0.03 to 0.13, $p = 0.031$), see Figure 3b. Tukey post-hoc tests confirmed that there were differences in apparent motion illusion between threatening and neutral stimuli for the obstacle shunning group (*Mdiff* = -0.49, *SE* = 0.056, $p < 0.001$ Bonferroni corrected), but not for the obstacle tolerance group (*Mdiff* = -0.079, *SE* = 0.056, $p = 0.96$). For a detailed overview of all of the contrasts see Supplementary Table 7.

T-tests then confirmed that, for the obstacle shunning group, neutral stimuli moved around the object ($t(479) = 5.05$, $p < 0.001$), and threatening stimuli moved through the object ($t(479) = -6.06$, $p < 0.001$, both of which significantly differed from zero.

For the obstacle tolerance group, however, perceptual biases did not differ significantly from zero for neutral ($p = 0.36$) or threatening stimuli ($p = 0.41$).

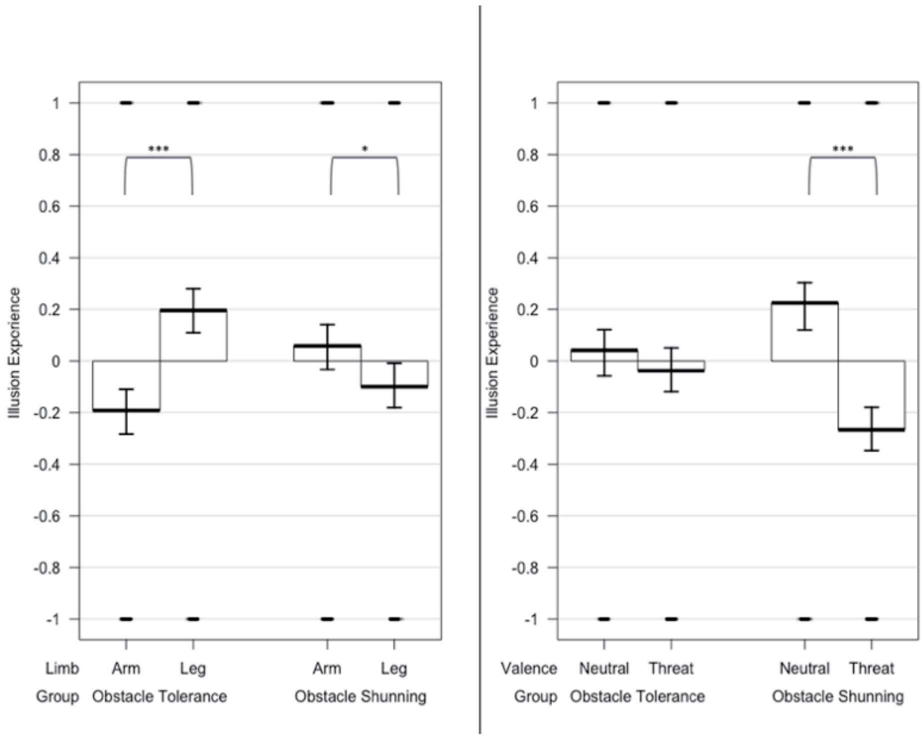


Figure 3. Apparent motion illusion amputee subgroups (object shunning vs object tolerance) in relation to (a) limb (arm / leg), and (b) valence (neutral / threatening).

DISCUSSION

In this study we sought to understand whether changes in the putative representations of the body following amputation are reflected in differences in body motion illusions. In line with several previous studies we replicated the effects of SOA, such that participants tended to perceive the depicted limb to move through objects when they flickered quickly (i.e., fast SOA), and around objects when they flickered more slowly (i.e., slow SOA). This indicates that the illusion was consistent with previous research that has shown that perception of apparent motion in body parts is driven by visual, motor and somatosensory constraints (and underlying neural networks) corresponding to one's own body representation (Stevens et al., 2000). Beyond the expected effects of SOA, the present study found nuanced differences in apparent motion paths perceived for arm and leg stimuli between amputees and non-amputees, and for threatening and neutral objects. Specifically, lower limb amputees perceived that legs moved around neutral stimuli and through threatening stimuli, whereas apparent motion for arms was not biased towards moving through or around objects. While non-amputees reported the same pattern of apparent motion for legs as the lower limb amputees (i.e., legs appeared to move around neutral and through threatening objects), non-amputees did perceive a bias for apparent motion of arms, which appeared to move through both neutral and threatening objects.

Within the lower limb amputee participants, we examined differences in apparent motion perception in relation to everyday phantom limb experience. Specifically, we investigated whether experiences of apparent motion varied as a function of whether the participant experienced obstacle "shunning" (i.e., the phantom disappears when occupying the same space as a physical object), or object "tolerance" (i.e., the phantom is unaffected when occupying the same space as a physical object). We expected that those who experience obstacle tolerance would have a greater tendency to experience obstacle tolerance in the experiment (i.e., motion paths *through* the object) regardless of SOA, compared with those who reported obstacle shunning in everyday life. While there was no interaction between group and SOA, failing to support this specific hypothesis, amputees who experienced obstacle shunning in daily life were found to have a perceptual bias to perceive legs to move *through* objects. This finding is consistent with the everyday experience that the phantom leg "shuns" co-existing with physical objects, essentially disappearing from awareness when occupying the same space as a physical object, thereby making it possible for the space formerly occupied by the phantom to now be occupied by a physical object without violating the laws of impenetrability. The opposite pattern was found for lower limb amputees who experience obstacle tolerance, such that they had a perceptual bias for legs to move around objects, despite their everyday experience that the phantom limb would not disappear if it occupied the same space as a physical object. This finding emphasises, however, that if the phantom limb does not disappear from awareness when occupying the same space as a physical object, their limb representation continues to pose a pseudo solidarity constraint as the limb (and the space that it is perceived to occupy) should avoid and move around physical objects.

Implications for implicit properties in body representations

As expected, all participants tended to perceive that the limb, whether an arm or a leg, followed the biologically feasible trajectory with a long SOA, apparently moving around the object. The trajectory violating solidarity or impenetrability constraints was more likely to be perceived with a short SOA, and in amputees who experience obstacle shunning. Thus, we replicated the robust SOA-dependent perceptions of apparent motion, and provided further insight into the role of top-down modulation of visual apparent motion of body parts (Shiffrar & Freyd, 1990; Stevens et al., 2000; Vannuscorps & Caramazza, 2016). In particular, we have shed further light on the framework that phenomenological bodily experience abides by the preservation of basic, implicit physical and cognitive perceptual rules that solid objects may not simultaneously occupy the space occupied by a body part. We have demonstrated that this violation may only arise when visual input indicates that this is the only feasible motion path (i.e., due to the time between static images) or when the putative body representations have preserved solidarity constraints that a *perceived* (not just physically present) body part cannot occupy the space of a physical object.

The present study examined whether the perception of apparent motion varied when the intermediate object was neutral (e.g., a broom) or threatening (e.g., a fire or saw). While we expected that threatening objects would enhance solidarity constraints, the expected threat-related effects were not observed, and instead legs appeared to move around, and arms through, both neutral and threatening objects for the non-amputee participants, with these same effects only being observed for leg stimuli in the amputee participants, with no bias in apparent motion path for threatening or neutral arm stimuli in amputees. These findings are difficult to explain, but may be due to nuanced effects of SOA that were washed out by averaging across fast and slow SOA. Alternatively, perhaps amputees have more variable experiences in apparent motion perception not just because of the solidarity constraints posed by the representation of the missing limb, but also due to alterations in the representation of body parts *other than* the amputated limb (Schwenkreis et al., 2003). Ultimately these effects should be further examined and replicated in future studies.

Amputees who reported obstacle tolerance in everyday life did not experience significant biases in apparent motion in relation to the threatening nature of objects, whereas amputees who experience obstacle shunning perceived the limb to move around neutral objects and through threatening objects, which was consistent with the effects observed in non-amputee participants. These divergent patterns suggest that the everyday tendency to experience a reduction in phantom limb vividness upon visual observation of the virtual limb's "collision" or co-location with a physical object (i.e., obstacle shunning) indicates that the limb may continue to be represented in a similar manner to a non-amputated limb. Given that these effects were observed only in amputees who experience obstacle shunning and in non-amputees, it suggests that when a perceived limb—whether phantom or not—ordinarily does not occupy the same space as an object, processes of motor planning, action execution or action observation may violate the laws of impenetrability when threatened. The implementation of an ecological paradigm where amputees with obstacle tolerance are asked to imagine moving their phantom (or the space occupied by their phantom) from one side of a threatening object to the other could provide further insight into this issue.

In our amputee group the illusion of apparent motion did not differ in relation to whether stimuli depicted a limb consistent with the side of the amputation. This is in contrast to previous findings in arm amputees for whom, irrespective of SOA, top-down constraints were influenced only when the visually observed limb corresponded to the amputated limb (Moseley & Brugger, 2009). However, it is notable that similar differences in the degree of lateralized sensorimotor representation of upper compared with lower limbs have been reported in the context of motor imagery (Ionta et al., 2007). This discrepancy may therefore have arisen because the repertoire of actions that can be executed with arms includes more precise lateralized movements (i.e. reaching, grasping, and writing) compared with the movements executed with the legs, which tend to be gross movements that are mainly for the purpose of bodily transportation, and maintaining posture and proprioception. While laterality constraints may be more strongly lateralized and precise for the hands (e.g., with respect to writing) than they are for the lower limbs (e.g., regarding bipedal movements during walking, or preferred foot to kick a ball), it was notable that preliminary sensitivity tests found no significant effects of stimulus laterality on apparent motion illusion. It therefore appears that stimulus laterality does not have a similarly crucial role in the experience of apparent motion in lower limb amputees, or non-amputee controls, as it does for upper limb stimuli in upper limb amputees.

Strengths, limitations and future directions

The strengths and limitations of the present study should be considered before drawing final conclusions. The present sample was relatively small, but larger than (or similar to) previous studies of apparent motion in amputees. Given the sample size, we took a robust multilevel approach to analysis that enabled us to model the variability both within and between subjects, providing us with sufficient power to interrogate our hypotheses with the available data. The cause and time since limb amputation varied, which could have led to more variable phantom sensations, both painless and painful, resulting in a sample of amputees with heterogeneous characteristics. It was notable, however, that obstacle shunning or tolerance was not associated with time since amputation. Future studies should examine whether apparent motion perception varies in relation to these other qualities of the phantom (e.g., whether it is painful or not), particularly in relation to perceived motion through or around threatening versus neutral objects.

When designing the present experiment, we attempted to generated a set of new images to depict apparent motion of human body parts in ecologically realistic situations that balanced extraneous features of the stimuli (i.e., setting, proximity, perspective). A downside to this approach was that the stimuli comprised a range of backgrounds, and varied proximity between the limb and the camera (ranging from < 1m to 2-3m). Moreover, while all images were photographed from the third person perspective, consistent with previous research, images where the body parts (particularly the arm stimuli) are more proximal to the camera may have been easier to *imagine* from the first person perspective, which may have influenced apparent motion paths. Future research should examine whether observing images from an egocentric, first-person perspective triggers more rapid motoric simulation of observed movements than those presented from an allocentric, third-person perspective given that the former result in different patterns of neural activity in the observer's visuo-motor system (Ruby & Decety, 2001). In particular, given that apparent motion percepts typically reflects the time taken for the limb to move from the position in the first image to that in the second image, the proximity and perspective of the limbs may influence the perceived motion path. Alternatively, some scenarios may make the illusion more or less convincing, vivid or consistent while holding SOA constant. Future studies should therefore examine the contribution of perspective and proximity on apparent motion experience across a range of SOAs, examine the precise SOA at which perception of short and long apparent motion paths switch.

Future studies should examine the neurophysiological mechanisms associated with apparent motion experience in both amputees and non-amputees by means of different indexes of arousal (e.g. pupil dilatation, or electroencephalography).

Although age significantly differed between the amputee and non-amputee participants, we found that it did not predict apparent motion experience. However, Somatosensory representations that underlie the illusory visuo-motor percept of the apparent motion illusion might be subject to qualitative changes across the age span given that healthy ageing leads to somatosensory alterations during motor imagery (Zapparoli et al., 2016), and degradation of motor system plasticity (Opie, et al., 2017). Future studies should specifically address the age-dependent effects on the perception of apparent motion.

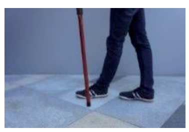
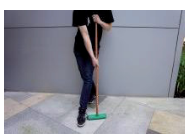
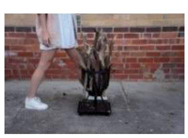
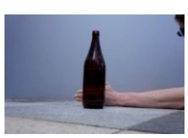
Amputees who reported that their phantom could not occupy the same location as a physical object indicated that they were aware of this experience "sometimes". The frequency and salience of these experiences is likely to be dependent on a range of factors, especially the frequency and intensity of phantom limb sensations, whether the amputee wears a prosthesis (during which object tolerance would not be possible by anything but the prosthesis), and how much the person focuses on their phantom limb during interactions with solid objects.

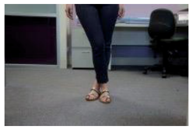
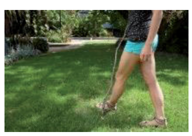
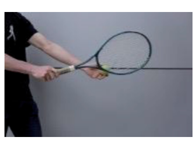
In conclusion, this study represents a first attempt to isolate object constancy properties of the phantom limb, and examined their relationship with visuo-motor perception of solidity constraints of body parts. We provide evidence of the potential role of sensorimotor representations in obstacle shunning versus obstacle tolerance in lower limb amputees. These body representations may have implications for visual motion perception. While the present study should be replicated in a larger sample, we observed that phantom limb experience may rest on visual-sensorimotor interactions in limb representations, which could critically influence everyday function, such as prosthesis adjustment. For instance, amputees with obstacle tolerance may be expected to better adjust to an artificial limb as "incorporation" of a prosthesis is arguably a precondition for its skilful use. Future studies might consider examining the association between prosthesis adjustment and apparent motion perception. The present findings highlight that the solidity constraints experienced in relation to a phantom limb (i.e., obstacle shunning or tolerance) are not a mere consequence of imagining the interaction between the phantom and an external object, but that these represent perceptually-driven phenomenon governing the interaction between one's bodily self and the world.

SUPPLEMENTARY MATERIALS

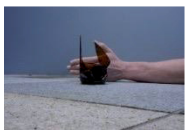
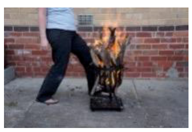
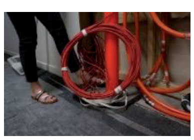
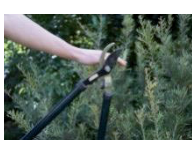
Supplementary methods

Supplementary Table 1. Overview of the neutral objects used in the illusion of apparent motion task and rated for their neutral-threatening nature on an 11-point scale during the pilot study (n=5) with (0)=pleasant object, (5)=neutral object, (10)=threatening object

Stimulus Number	Picture of Object	Description	*M (SD)*
1		Arm over arm	3.80 (1.91)
2		Broom handle	3.95 (1.88)
4		Cricket bat	3.60 (2.42)
6		Broom	4.05 (1.76)
7		Hand broom	4.05 (1.70)
11		Fire pit	5.15 (1.63)
15		Bottle	4.85 (1.81)

20		Heater switched off	5.60 (1.90)
24		Leg over leg	3.75 (1.92)
26		Plant	3.25 (1.97)
27		Hand shovel	3.25 (1.74)
28		Putty gun	3.95 (1.57)
29		Hand shovel	4.85 (2.03)
30		Stick	3.20 (1.67)
31		Tennis racket	2.85 (2.08)
32		Umbrella	4.15 (1.81)

Supplementary Table 2. Overview of all different threatening objects used in the illusion of apparent motion task and rated for their neutral-threatening nature on an 11-point scale during the pilot study (n=5) with (0)=pleasant object, (5)=neutral object, (10)=threatening object

Stimulus Number	Picture of Object	Description	*M (SD)*
3		Axe	6.50 (1.76)
5		Broken glass	8.00 (1.62)
9		Fire	8.25 (1.20)
10		Cactus	5.25 (2.51)
12		Gardening tool	5.70 (2.08)
13		Electric wire	6.00 (1.89)
14		Fan	7.00 (1.62)
16		Gardening scissors	7.25 (1.77)

17		Gardening scissors	8.00 (1.65)
18		Hand drill	7.95 (1.54)
19		Paper cutter	8.05 (1.85)
21		Heater switched on	7.25 (1.89)
22		Hand saw	8.15 (1.57)
23		Knife	8.00 (1.38)
25		Hand saw	7.80 (1.47)
33		Brush cutter	6.85 (2.11)

Supplementary Results

Sensitivity analyses: Non-amputee controls

Model 1 included fixed factors of stimulus Laterality, Valence, SOA and Limb, interaction effects between stimulus laterality and valence, SOA and limb, and random intercepts for participant ID. The interaction effects were modeled to characterize illusion perception in non-amputees before examining group differences, which has not previously been examined. Model 1 had the following formula, where "β_x" represents the estimated parameters, "*e*" represents the normally distributed residuals, and "*p*" represents the random effects: *intercept* + *p* + β_1 *(Laterality)* + β_2 *(Valence)* + B_3 *(SOA)* + B_4 *(Limb)* + B_5 *(Laterality*Valence)* + B_6 *(Laterality* SOA)* + B_7 *(Laterality*Limb)* + *e*.

There was no main effect of stimulus Laterality (b=0.11, t(2216) = 1.547, 95% CI: -0.03 to 0.25), nor were there interactions for Laterality x Limb (b < -0.0001, t(2216) = 0, 95% CI: -0.14 to 0.14), Laterality x Valence (b = 0.05, t(2216) = 0.699, 95% CI: -0.09 to 0.19), Laterality x SOA (b = -0.57, t(2216) = -0.798 , 95% CI: -0.20 to 0.08), and repeated measure were confirmed to be non-independent (ICC(1) = 0.24, F(13,2226) = 50.93, p < 0.0001).

There was a strong main effect of the SOA (b = -0.38, t(2216) = -5.24, CI 95%: -0.52,-0.23, p < 0.0001] for apparent motion bias perception replicating the effect of SOA, whereby a short SOA elicited a bias towards passing through the solid object (*m* = -.264, *se* = .028), and a long SOA elicited a bias towards passing around the solid object (*m* = .028, *se* = .029). The bias was evidently stronger for the short SOA than the long SOA, which was fairly close to chance. Supplementary Table 3 offers a complete overview of all the observed fixed effects in control participants.

Supplementary Table 3

Fixed effects	*b*	*Lower Bound*	*Upper Bound*	*SE*	*df*	*t*	*p*	
(Intercept)	0.03	-0.26	0.32	0.14	18	0.22	0.825	
Laterality	0.11	-0.03	0.25	0.07	2216	1.55	0.122	
SOA	-0.38	-0.52	-0.24	0.07	2216	-5.24	< 0.0001	***
Valence	-0.16	-0.30	-0.02	0.07	2216	-2.30	0.022	*
Limb	0.18	0.04	0.32	0.07	2216	2.55	0.011	*
Laterality*SOA	-0.06	-0.20	0.08	0.07	2216	-0.80	0.425	
Laterality*Threat	0.05	-0.09	0.19	0.07	2216	0.70	0.485	
Laterality*Limb	< 0.001	-0.14	0.14	0.07	2216	0.00	0.999	
SOA*Valence	0.09	-0.05	0.23	0.07	2216	1.30	0.195	
SOA*Limb	0.13	-0.01	0.27	0.07	2216	1.80	0.073	.
Valence*Limb	-0.32	-0.46	-0.18	0.07	2216	-4.49	< 0.0001	***

Notes: Valence (0 = neutral, 1 = threatening), Limb (0 = Arm, 1 = Leg), SOA (0 = slow, 1 = fast), Stimulus Laterality (0 = left, 1 = right)

As previous studies have predominantly focused on upper limb stimuli, we examined whether there were laterality effects for the leg stimuli in the control group. We fit a final linear mixed model including as fixed factors Leg laterality (left/right), SOA (fast/slow), Valence (threatening/neutral) and the two-way interactions between these factors. The data only a trend for the factor leg stimulus laterality ($b = 0.11071$, $t(2220) = 1.776.$, $p < 0.\ 0.076$), see Supplementary Table 4 for all observed fixed effects.

Supplementary Table 4

Fixed effects	*b*	*Lower Bound*	*Upper Bound*	*SE*	*df*	*t*	*p*	
(Intercept)	0.12	-0.16	0.40	0.14	16	0.89	0.389	
SOA	-0.31	-0.43	-0.19	0.06	2220	-4.99	< 0.0001	***
Valence	-0.33	-0.45	-0.20	0.06	2220	-5.21	< 0.0001	***
Laterality	0.11	-0.01	0.23	0.06	2220	1.78	0.076	.
SOA*Valence	0.09	-0.05	0.23	0.07	2220	1.29	0.197	
SOA*Laterality	-0.06	-0.20	0.08	0.07	2220	-0.79	0.427	
Valence*Laterality	0.05	-0.09	0.19	0.07	2220	0.70	0.487	

Notes: Valence (0 = neutral, 1 = threatening), Limb (0 = Arm, 1 = Leg), SOA (0 = slow, 1 = fast), Stimulus Laterality (0 = left, 1 = right)

Sensitivity analyses: Amputees

Model 1 comprised fixed effects of missing limb laterality (left / right) and stimulus laterality (left /right), valence (threatening / neutral), SOA (short / long), limb (arm / leg), and interactions between missing limb and stimulus laterality, and random intercept for participant ID to account for within person dependence. Model 1 had the following formula, where "β_x" represents the estimated parameters, "*e*" represents the normally distributed residuals, and "*p*" represents the random effects: *intercept + p + β_1 (Missing Limb laterality) + β_2 (stimulus Laterality) + β_3 (Valence) + B_4 (SOA) + B_5 (Limb) + B_6 (Missing Limb laterality* stimulus Laterality) + e.*

This model showed that missing Limb (b = 0.12, t(10) = 0.39, 95% CI: -0.46 to 0.69, p = 0.70), stimulus laterality (b = 0.06, t(1903) = 0.978, 95% CI: -0.06 to 0.18), and the interaction between missing limb laterality and stimulus laterality (b = -0.04, t(1903) = -0.524, 95% CI: -0.20 to 0.12, p = 0.60), did not predict illusion ratings. However, variability in the illusion ratings were significantly explained by fixed factors of stimulus Valence (b =-0.28542, t(1903) =-7.20, CI 95% = -0.36 to -0.21), SOA (b = -0.27, t(1903) = -6.784, CI 95%: -0.35 to -0.19) and Limb (b = 0.11, t(1903) = 2.892 , CI 95%: 0.04 to 0.19) and repeated measures were confirmed to be non-independent (ICC(1) = 0.22, F(11, 1908) = 46.41, p. < 0.001).

A second model explicitly contrasted with a model excluding the parameters *β_2 (Laterality)* and *B_6 (Missing Limb*stimulus Laterality)* and examining the change in -2 log-likelihood (Bliese & Ployhart, 2002). There was no significant change in model fit between models ($\chi^2(2)$ = 1.08, p = 0.58), showing that laterality did not contribute to illusion experience in amputees.

Full output for primary hypothesis testing

Analysis of apparent motion illusion in amputees vs controls

Supplementary Table 5. Final linear mixed model including predictors Group (amputee / control) SOA (short / long), stimulus valence (threat / neutral), and stimulus limb (arm / leg) and the two and three ways interactions. The dependent variable is the illusion bias score.

Fixed effects	*b*	*Lower Bound*	*Upper Bound*	*SE*	*df*	*t*	*p*	
(Intercept)	0.08	-0.19	0.35	0.14	30	0.60	0.552	
Groups	-0.01	-0.40	0.39	0.20	30	-0.03	0.980	
SOA	-0.40	-0.53	-0.26	0.07	4121	-5.83	< 0.0001	***
Valence	-0.13	-0.26	0.00	0.07	4121	-1.93	0.054	.
Limb	0.19	0.06	0.32	0.07	4121	2.82	0.005	**
Groups*SOA	0.12	-0.06	0.30	0.09	4121	1.33	0.183	
Groups*Valence	0.08	-0.11	0.25	0.09	4121	0.81	0.416	
SOA*Valence	0.08	-0.10	0.25	0.09	4121	0.85	0.398	
Groups*Limb	0.24	0.06	0.42	0.09	4121	2.58	0.010	*
SOA*Limb	0.11	-0.06	0.29	0.09	4121	1.25	0.213	
Valence*Limb	-0.34	-0.51	-0.16	0.09	4121	-3.79	< 0.0001	***
Groups*SOA*Valence	0.00	-0.21	0.21	0.11	4121	0.03	0.978	
Groups*SOA*Limb	-0.20	-0.41	0.01	0.11	4121	-1.88	0.060	.
Groups*Valence*Limb	-0.22	-0.42	-0.01	0.11	4121	-2.04	0.042	*
SOA*Valence*Limb	0.04	-0.17	0.24	0.11	4121	0.33	0.743	

Notes: Valence (0 = neutral, 1 = threatening), Limb (0 = Arm, 1 = Leg), SOA (0 = slow, 1 = fast), Stimulus Limb (1 = left, 2 = right)

Supplementary Table 6. Simultaneous Tests for General Linear Hypotheses. Multiple Comparison (Tukey Contrasts) for the interaction Group*Valence*Limb

Linear Hypothesis					*Mdiff*	*SE*	*adjusted p value (Bonferroni)*	
Amputee Neutral Arm	-	Control Neutral Arm	=	0	0.056	0.197	1.000	
Control Threat Arm	-	Control Neutral Arm	=	0	-0.093	0.052	1.000	
Amputee Threat Arm	-	Control Neutral Arm	=	0	0.039	0.197	1.000	
Control Neutral Leg	-	Control Neutral Arm	=	0	0.246	0.052	< 0.0001	***
Amputee Neutral Leg	-	Control Neutral Arm	=	0	0.439	0.197	0.727	
Control Threat Leg	-	Control Neutral Arm	=	0	-0.168	0.052	0.032	*
Amputee Threat Leg	-	Control Neutral Arm	=	0	-0.115	0.197	1.000	
Control Threat Arm	-	Amputee Neutral Arm	=	0	-0.149	0.197	1.000	
Amputee Threat Arm	-	Amputee Neutral Arm	=	0	-0.017	0.056	1.000	
Control Neutral Leg	-	Amputee Neutral Arm	=	0	0.190	0.197	1.000	
Amputee Neutral Leg	-	Amputee Neutral Arm	=	0	0.383	0.056	< 0.0001	***
Control Threat Leg	-	Amputee Neutral Arm	=	0	-0.224	0.197	1.000	
Amputee Threat Leg	-	Amputee Neutral Arm	=	0	-0.171	0.056	0.061	.
Amputee Threat Arm	-	Control Threat Arm	=	0	0.132	0.197	1.000	
Control Neutral Leg	-	Control Threat Arm	=	0	0.339	0.052	< 0.0001	***
Amputee Neutral Leg	-	Control Threat Arm	=	0	0.532	0.197	0.195	
Control Threat Leg	-	Control Threat Arm	=	0	-0.075	0.052	1.000	
Amputee Threat Leg	-	Control Threat Arm	=	0	-0.022	0.197	1.000	
Control Neutral Leg	-	Amputee Threat Arm	=	0	0.207	0.197	1.000	
Amputee Neutral Leg	-	Amputee Threat Arm	=	0	0.400	0.056	< 0.0001	***
Control Threat Leg	-	Amputee Threat Arm	=	0	-0.207	0.197	1.000	
Amputee Threat Leg	-	Amputee Threat Arm	=	0	-0.154	0.056	0.160	
Amputee Neutral Leg	-	Control Neutral Leg	=	0	0.193	0.197	1.000	
Control Threat Leg	-	Control Neutral Leg	=	0	-0.414	0.052	< 0.0001	***
Amputee Threat Leg	-	Control Neutral Leg	=	0	-0.361	0.197	1.000	
Control Threat Leg	-	Amputee Neutral Leg	=	0	-0.607	0.197	0.058	.
Amputee Threat Leg	-	Amputee Neutral Leg	=	0	-0.554	0.056	< 0.0001	***

Analysis of apparent motion illusion in Obstacle Shunning group vs Obstacle tolerance group

Supplementary Table 7Final linear mixed model including predictors Group (Obstacle Shunning group / Obstacle Tolerance group), SOA (short / long), stimulus valence (threat / neutral), and stimulus limb (arm / leg) and the two and three ways interactions. The dependent variable is the illusion experience.

Fixed effects	*b*	*Lower Bound*	*Upper Bound*	*SE*	*df*	*t*	*p*	
(Intercept)	-0.10	-0.52	0.32	0.22	12	-0.45	0.663	
Group	0.33	-0.26	0.92	0.31	12	1.07	0.305	
SOA	-0.32	-0.52	-0.13	0.10	1895	-3.18	0.001	**
Valence	0.11	-0.09	0.31	0.10	1895	1.09	0.277	
Limb	0.63	0.43	0.83	0.10	1895	6.18	< 0.0001	***
Group*SOA	0.15	-0.11	0.41	0.1	1895	1.10	0.273	
Group*Valence	-0.29	-0.55	-0.03	0.1	1895	-2.16	0.031	*
SOAfast*Valence	0.05	-0.21	0.31	0.1	1895	0.35	0.730	
Group*Limb	-0.35	-0.61	-0.09	0.13	1895	-2.67	0.008	**
SOA*Limb	-0.05	-0.31	0.21	0.13	1895	-0.41	0.684	
Valence*Limb	-0.49	-0.75	-0.23	0.13	1895	-3.67	< 0.0001	***
Group*SOA*Valence	-0.03	-0.33	0.28	0.15	1895	-0.16	0.871	
Group*SOA*Limb	-0.16	-0.46	0.14	0.15	1895	-1.03	0.302	
Group*Valence*Limb	-0.23	-0.53	0.08	0.15	1895	-1.47	0.143	
SOA*Valence*Limb	0.13	-0.18	0.43	0.15	1895	0.82	0.415	

Notes: Valence (0 = neutral, 1 = threatening), Limb (0 = Arm, 1 = Leg), SOA (0 = slow, 1 = fast), Stimulus Limb (1 = left, 2 = right

GENERAL DISCUSSION

The experience of having a body is at the center of our self. Self and body are two terms pointing to an inseparable relationship. We identify our self with our body, and our body provides the space for our self to be. However, the general rule that the bodily borders delimited by flesh and bones constrain the experience of our self may, in some cases, no longer apply. In my thesis, I provided neural and behavioral examinations of some of these cases. Each study captured a peculiar aberration of bodily experience.

- Study 1 examined **body integrity dysphoria**; a developmental and long-lasting condition whereby non-psychotic individuals seek a limb's amputation to restore their identity, reconciling the apparent contradiction between their perceived fully-limbed and their desired amputated body.

- Study 2 examined **somatoparaphrenia**, i.e., the case of brain-damaged persons claiming that a plegic limb belongs to someone else. Somatoparaphrenia is a rare and temporary neuropsychological condition. It poses a shred of fascinating evidence that the feeling of non-belonging, also observed in persons with body integrity dysphoria, might be "compensated" by the presence of a person.

- Study 3 examined **asomatognosia.** Following brain damage, the contralesional limbs may be dramatically experienced as no longer existing. This experience needs to be referred to as a bodily or somesthetic experience. The affected limbs are indeed still accessible to visual awareness.

- Study 4 examined **phantom limb sensations**. These sensations, postural and motor in nature, manifest themselves, among other conditions, after the amputation of a limb. Phantom limb sensations refer to the self as extending beyond the space delimited by flesh and bones. They are felt in the extracorporeal space as "ghostly" or "invisible" products of the mind. The focus of study 4 was on the clinical assessment of phantom limb sensations and on gathering new experimental paradigms to capture individual differences in these sensations.

- Study 5 zoomed in on how phantom limb sensations interact with physical matter co-located in the space. In the case of ***obstacle shunning***, the phantom limb bends back or disappears when it comes into contact with an object. In contrast, in the case of ***obstacle tolerance***, the phantom is felt within the object, thus violating the basic physical law of the impenetrability of two solid objects in the space.

In this section, I shall discuss the rationale, the methods, the results, the implications, the strengths, and the limitations of each study. Then, referring to one of the two aims, i.e., to design tools for the clinical assessment and the experimental investigation of bodily self disorders, I will propose reflections based on own scientific data on the implementation of the apparent motion task with human body parts as stimuli. This task was newly implemented in the present thesis for the investigation of disorders of the bodily self. For the other aim of the thesis, i.e., to shed new light on the neural and behavioral aspects underlying the bodily self, I will propose a neurofunctional model for the bodily self. This model encompasses my own and previous studies' findings from the analyses of the varieties of bodily experience analyzed in the present thesis.

Study 1. Body Integrity Dysphoria

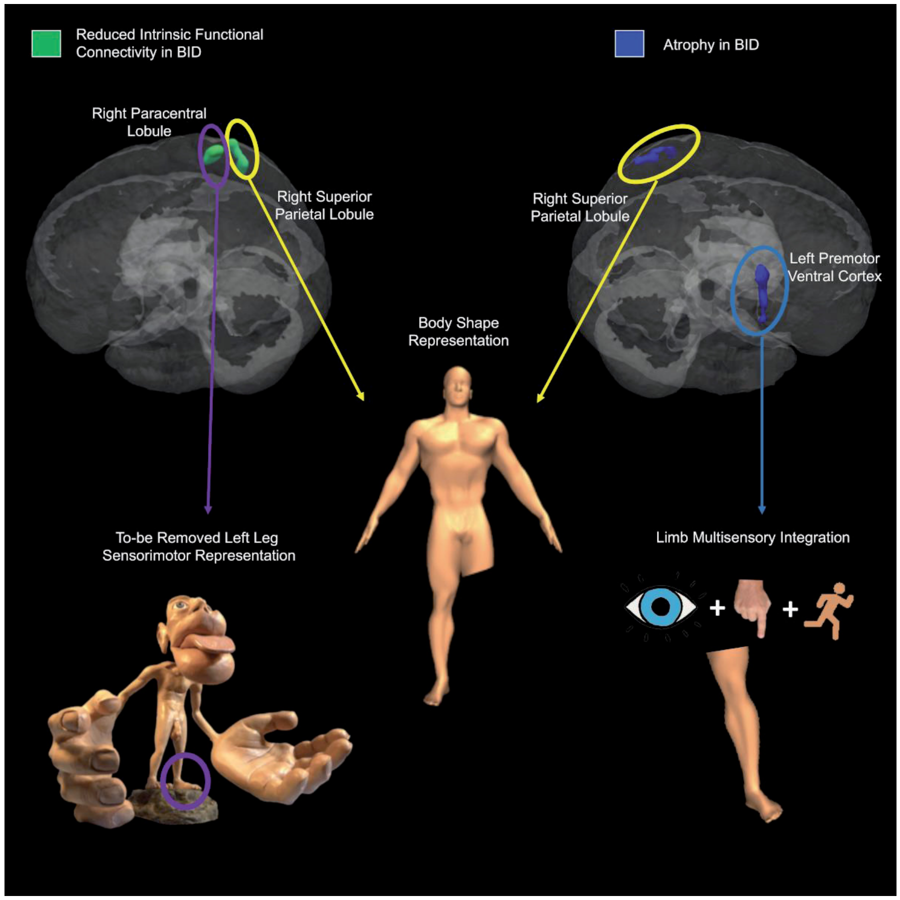
Rationale. Body Integrity Dysphoria (BID) was previously studied as a paraphilia or an internet-induced madness (Peter Brugger et al., 2016). Some medical authorities even considered it not to be worthy of being investigated at all. Scientists and laypersons alike may indeed only believe in the existence of a sign or a syndrome once it can be pinpointed to the brain surface. In the wake of the new release of ICD-11[1], which proposes to define BID as a "disorder of bodily distress or bodily experience", we felt it was necessary to explore the systematic neural correlates of this condition. Our methodological approach also considered that previous neuroimaging studies focused either on local structural changes or brain connectivity, and mostly in rather few individuals with different limbs as the target of the amputation need (Hänggi et al., 2016, 2017; Hilti et al., 2013; McGeoch et al., 2011; van Dijk et al., 2013). We presented data on both function (connectivity) and structure in 16 men who aimed for an amputation of the left leg. Sixteen healthy men matched for age and education functioned as controls. This was by far the largest sample in the scientific literature.

Methods. We looked at the altered cortical hubs of functional connectivity in BID. Cortical hubs are small brain areas that, despite their reduced spatial extension, present with a relatively high number of functional connections with all the other brain areas (Buckner et al., 2009; Rubinov & Sporns, 2010; Sporns et al., 2007). We used the intrinsic functional connectivity index, which quantifies, for each brain voxel, the strength of the connectivity with all the other brain voxels (Martuzzi et al., 2011). The strength of the functional connectivity is defined by the correlation between the time-series of activations of these voxels while the participants let their minds wander. For

[1] The manual of the International Classification of Diseases (ICD) is used by the medical community to report diseases, disorders, injuries and other related health conditions for all the clinical and research purposes conforming ro standardized and internationally valid diagnostic criteria.

the structural analyses, we looked at the atrophies and hypertrophies in BID. We used voxel-based morphometry, which allowed for the quantification of the concentration of the gray matter in each brain voxel.

Results and implications. The results, displayed in the graphical abstract below, were the following: i) in BID, the brain area containing the sensorimotor representation of the affected limb, the right paracentral lobule, showed a breakdown in functional connectivity; ii) the left premotor ventral cortex typically involved in multimodal limb integration (Blom et al., 2016; Ehrsson et al., 2005a; van Dijk et al., 2013) was found to have a reduced concentration of gray matter; iii) the right superior parietal lobule representing the body image (McGeoch et al., 2011; Vilayanur S. Ramachandran et al., 2009) showed both a breakdown in functional connectivity and reduced concentration of gray matter; iv) the less concentration of gray matter in the right superior parietal lobule, the more an individual with BID would mimic the status of an amputee. The purpose of this "pretending behavior" is presumably to resolve the mismatch between the actual and desired body shape. Since birth, the latter is purportedly hard-wired in the brain, as the desire of amputation is present as long as the BID individual can remember. Taken as a whole, these results suggest that limb ownership depends on (1) the functional connectivity of the brain area containing its primary sensorimotor representation and (2) the structural and functional integrity of areas representing the body as a whole. A breakdown at both levels is observed in persons who aim for the amputation of a healthy limb.



Graphic abstract. Summary of the functional connectivity and gray matter density results in BID individuals

Strengths and limitations. As also noticed by Longo in his commentary to our study (Longo, 2020), despite the fact that our study has far-reaching implications for the understanding of body integrity dysphoria and for the neural aspect of the bodily self in general, its sample size, in absolute terms, remains modest. Only through more than 10 years of cooperation between different international research centers has it been possible to put together a relatively substantial database of individuals willing to participate in BID research, considering the rarity and secrecy of the disorder. A number of 16 individuals can therefore still be considered impressive, given the circumstance. Furthermore, results survived conservative statistical thresholding.

Study 2. Somatoparaphrenia

Rationale. Previous studies addressed the neural correlates of somatoparaphrenia by localizing and quantifying the amount of lesioned brain tissues in affected individuals (Gandola et al., 2012; Invernizzi et al., 2013; Moro et al., 2016; Romano et al., 2015). While the anatomo-clinical correlational methods they implemented were useful to spot the brain areas whose degradation is supposed to be a precondition for the clinical picture to ensue, they do not point to the brain activity related to a specific component of the disorder. Functional magnetic resonance imaging (fMRI) is better suitable for this purpose. In this study, we recorded the activity related to the productive component of somatoparaphrenia, i.e., limb misattribution to someone else. Previous studies suggested that somatoparaphrenia might be accounted for by a disturbance in interhemispheric communication (Halligan et al., 1995). The empirical approach taken in this study allowed for the explicit testing of this hypothesis. Resting-state fMRI (rs-fMRI) was additionally used to map the dysfunctional neural networks of somatoparaphrenia.

Methods. We studied the case of S.P.P., a 76 year-old man who suffered a right hemisphere ischemic stroke, leaving him with large lesions of both cortical and subcortical gray and white matter. S.P.P. denied ownership of his left paralyzed hand and claimed that it belonged to his mother. To map the brain activity distinctly linked to the content of the delusion, in a block-designed fMRI motor imagery task, S.P.P. was asked to imagine to open/close the intact right hand (MI R), the left paralyzed hand under own volitional control (MI L_{own}), and the left paralyzed hand *as moved by his mother* (MI L_{mother}). We subtracted the MI R activity from that of MI L_{mother}, and the MI L_{own} activity from that of MI L_{mother},. Detection of the overlap between these two contrasts brought about the localization of the brain activity due to the productive component, which constituted the net activity from the motor task. To reconstruct the alteration in S.P.P.'s functional connectivity, S.P.P. and 21 controls matched for age and formal education underwent a separate resting-state fMRI experiment. We tracked the functional connectivity with a classic seed-to-voxel approach (i.e., correlation of the blood-oxygen-level-dependent signal extracted from the seed with that of all the resting brain voxels in the time series). Our seeds were i) the area linked to the productive component and ii) the affected hand sensorimotor network.

Results and implications. For the fMRI motor imagery task, subtraction of the MI L_{own} and MI R activities from that of MI L_{mother} resulted in a circumscribed activation of the pars opercularis of the right inferior frontal gyrus (rIFG). Regarding the resting-state functional connectivity analyses in S.P.P., we found that i) the affected hand sensorimotor network was disconnected from the left secondary somatosensory cortex, ii) the activity at the rest of rIFG was anticorrelated with that of the left fronto-parietal mirror network, i.e., the homologous area in the left hemisphere (Broca area/frontal pole) and with that of the left temporo-parietal junction. Increasing evidence suggests that the rIFG is responsible for the integration of the contralateral limb sensory input (i.e., the integration of spatial location, visual, tactile, vestibular, and re-afferent motor signals) departing from the primary somatosensory and motor areas (Ehrsson et al., 2004, 2005a; Tsakiris et al., 2007b). The multisensory limb integration represents a crucial process for anchoring the limb to the implicit and continuously updated representation of location, motion in space and time, and orientation of body parts, i.e., the body schema (Head & Holmes, 1911). Intact multisensory integration and intact body schema form the basis of a coherent bodily self and accurate limb self-attribution (Blanke, 2012). Our findings clearly show that the limb misattribution can be, at least to some extent, ascribed to a circumscribed alteration of the multisensory integration areas of the brain: the rIFG. Furthermore, in accordance with the results of study 1, we also show that the denial of limb ownership may depend, from a neural point of view, on the disruption of functional connectivity of this limb's primary sensorimotor area. Finally, we show that when the rIFG is active at rest, the route to verbal access in the left hemisphere is not available, as shown by the deactivation of the Broca area and the left temporo-parietal junction. Our results fit the model proposed by Halligan et al. (1995). This model maintains that the confabulation originates from a narrator's attempt (associated with left hemisphere activity), to "make up a story", elaborating the distorted sensorimotor information coming from the lesioned right hemisphere. Our findings add an important piece of knowledge to the previous literature by specifying where in the brain this narrator in left hemisphere.

Strengths and limitations. One may argue that S.P.P. had not been capable of imagining the open/close hand movements. While the present study lacks precise electromyographic measures, we looked at the MI L_{own} and the MI R activities separately. We found that S.P.P. was recruiting the typical motor imagery networks and the areas for body representation. Furthermore, generalization of the results also requires caution. This is a single-case study. Notably, however, S.P.P. was a remarkable case in that he was presenting no delusion about his motor capacity, i.e., presented no anosognosia for hemiplegia. This allowed for implementing the motor imagery task to tap into the content of the somatoparaphrenic delusion, without contamination from delusions of a different kind. Moreover, a particular strength of the present findings is that the focal activation of the rIFG across different contrasted conditions survived conservative statistical thresholds.

Study 3. Asomatognosia

Rationale. Two main reasons motivated the conduct of the present study. One was to provide a rigorous definition of asomatognosia for the clinical and scientific literature. The second was to employ a chronometric task to tap into the characteristics of sensorimotor representations underlying the limb felt as absent. Concerning the first aim, the nosological classification of asomatognosia as a disorder of body schema had indeed for a long time been undisputed. However, a few but influential reports introduced a bias in the literature by arbitrarily proposing the denial of ownership of the limb as the core symptom of asomatognosia (Feinberg et al., 2010). In other terms, asomatognosia was mistaken for a "mild form" of somatoparaphrenia. However, while comorbidity with symptoms of non-recognition or misrecognition of a body part is relatively frequent, the feeling of absence of a limb remains the defining feature of asomatognosia (Jenkinson et al., 2018). In the present study, we offered a template for a standardized clinical interview that captures the core symptoms of asomatognosia, but separates them from the associated ones (see appendix 1). Concerning the second aim, we administered a patient newly affected by pure somesthetic asomatognosia a well-established task, i.e., the limb laterality judgment task (Parsons, 1987), which I will describe below.

Methods. We studied the case of ASG, a 53-year-old right-handed lady. After the removal of an intraventricular meningioma in the right atrium, she presented with a large right temporo-parietal-occipital lesions, also involving the underlying white matter. Four to 5 months from the surgery, the left half of her body intermittently “felt not just numb or unresponsive to touch, but no longer present at all". However, over a few weeks, this feeling became less frequent and was restricted to the left *lower* limb. ASG underwent a limb laterality judgment task. Additionally, 10 healthy controls were tested with the same task. Hands and feet rotated at different angles were presented at the center of the screen. Participants were asked to indicate whether the shown picture corresponded to a right or a left limb by pressing a response key congruently with either the right or the left index finger. Speed and accuracy were stressed to be of equal importance. Stimuli were shown once in volar and once in dorsal view. According to Parson's comparative method (Parsons, 1987), this task requires the activation of two processes. First, the selection of the sensorimotor representation of either the right or left limb, and then the mental maneuver of this sensorimotor representation to match the position of the depicted hand. The execution of this task relies on the integrity of the participant's body schema. Indeed, many studies showed that the analysis of the time required to provide a laterality judgment (reaction times – RTs) is affected by the participant's limb posture and biomechanical bodily constraints (e.g., Zapparoli et al., 2014, 2016).

Results and implications. ASG's performance on the task was found to be as accurate as of that of the controls. However, compared with the controls, ASG' RTs were significantly longer, specifically for *left feet*. The observed RTs pattern is compatible with ASG's clinical symptomatology. Indeed, ASG's experience of a body part as ceasing to exist was exclusively involving the *left foot* during the very same week she had performed the task. Longer RTs had also previously been considered a trojan horse in detecting ongoing cortical reorganization processes and alterations in the body schema. For example, longer RTs are observed in patients with complex regional pain syndrome (CRPS) specific for the *painful* hand (Moseley, 2004). CRPS syndrome is characterized by a profound cortical reorganization and neglect-like sensory and visuo-spatial attention exploration deficits that are reflected in the phenomenal experience that a "limb feels foreign" (Förderreuther et al., 2004; Galer & Jensen, 1999). ASG's longer RTs for the left foot may suggest a specific alteration in the body schema in asomatognosia. Importantly, RTs were longer, especially for feet shown in the volar view. Previous studies showed that hands presented with the palms facing up require the manipulation of the respective motor representation while hands with palms facing down are more likely to be visually processed (Zapparoli et al., 2014). While, admittedly, this view-dependent effect had not been explicitly tested for the mental rotation of feet, ASG's RT pattern for feet may reflect the type of left-sided hemiasomatognosia affecting specifically somesthetic but not visual awareness. Our results confirm that the implicit task we administered is sensitive to detect core features of disturbances of the bodily self by chronometric means.

Strengths and limitations. One important limitation of study 3, which also applied to study 2, is that only one single patient had been tested. Future studies need to recruit more patients. However, the clinical picture of asomatognosia in ASG was pure, i.e., she did not present associated symptoms such as anosognosia for hemiplegia and somatoparaphrenia. Another limitation is that the cortical reorganization and alteration of the body schema in asomatognosia are only deducted from the behavioral performance in the limb laterality judgment task. Future fMRI studies should look at the neural correlates of asomatognosia by using a similar task in similar patients.

Study 4. Phantom limb sensation

Rationale. In recent years, remarkable advances have taken place for the design of high-tech hand prostheses that could stand-in for the missing hand's functionality, at least to some extent. Yet, there is dramatic evidence for rejection and abandonment of prostheses in a considerable number of amputees (e.g., Resnik et al., 2020 for a recent account). A key aspect for the integration of the prosthesis in the bodily self concerns the way the prosthesis (i.e., physical matter in the space beyond the visible borders of the residual limb) interacts with a mind product such as a phantom limb. Efficient interaction between mind and matter requires the characterization of the individual differences in phantom limb sensations. However, previous studies largely neglected the systematic investigation of phantom limb sensations as heterogeneous phenomena connotated by highly inter-individual and intra-individual variability. The aim of study 4 was to fill this gap in the literature. We recruited 15 upper limb amputees with phantom limb sensations and 29 intact controls. We supplied the scientific community with data from clinical interviews, clinical exams and scientific experiments for the neurocognitive examination of individual differences in phantom limb sensations, as described in 4 datasets below. Both clinical interviews and scientific experiments were conducted within the MeganePro project (Myo-Electricity, Gaze and Artificial-intelligence for Neurocognitive Examination & Prosthetics); an interdisciplinary and multicenter project aimed at (i) improving the control of myoelectric hand prostheses and (ii) understanding the neurocognitive alterations and clinical parameters in hand amputees.

Methods.

MeganePro dataset "Clinical Interview and Neurocognitive Tests in Amputees" contains quantitative and qualitative data on phantom limb sensations collected during a 2 h clinical interview. Information on non-painful (i.e., length, girth, position in space, and changes over time, temperature sensations, spontaneous and intentional movement of the phantom hand) and painful phantom limb sensations are gathered. Associated phenomena such as body representation in dreams, impact on the quality of life, among others, are also examined.

- MeganePro dataset 2 contains multimodal data (gaze, surface electromyography, accelerometry, and behavioral) from an experiment where amputees were asked to imagine performing visually-guided pointing movements with their phantom limb. This experiment tapped into the eye-phantom limb coordination.

- MeganePro dataset 4 contains multimodal data (gaze, surface electromyography, accelerometry, and behavioral) from an experiment where amputees were asked to imagine or reposition the phantom limb from a starting to an endpoint, either passing *around* or *through* an "obstacle" in-between these starting and endpoints. Obstacle shunning and obstacle tolerance are here for the first time characterized quantitatively in a setting reproducing an everyday life situation.

Results and implications. In contrast to studies 1-3 and study 5 discussed below, the focus of the present study was on sharing meaningful and high-quality data with the scientific community to characterize individual differences in phantom limb sensations. With this study, we fully embraced an open science spirit and the practice of publicly sharing the clinical and scientific data and scripts used for data analyses. Accordingly, instead of testing specific hypotheses, the analyses we had performed and shared addressed the quality of the data. The results of these validation analyses encourage the use of the dataset for further hypothesis testing.

Strengths and limitations. Some researchers may find explorations not directly testing a hypothesis of limited value. However, the present contribution was framed from the beginning as a comprehensive description of clinically and scientifically valuable datasets. The final products were derived from the interaction of worldwide renowned experts from various backgrounds related to phantom limb sensations, such as neuropsychology, Prof. Dr. Peter Brugger (University Hospital of Zurich), hand surgery, Prof. MD. Franco Bassetto (University Hospital of Padova), and prosthetic control, Prof. Ing. Henning Müller and Dr. Manfredo Atzori (HES-SO Valais-Wallis).

Given the multifaceted nature of the dataset we offered, we believe that its sharing could trigger the researchers' interest in all these communities. We hope that it will bring about significant advances in all these fields.

Study 5. Phantom limb sensation: Obstacle shunning and Obstacle Tolerance, and apparent motion perception

Rationale. Although obstacle shunning and obstacle tolerance are well-known among clinicians as phenomenal peculiarities of phantom limb sensations, they are poorly understood on a scientific level. This lack of understanding is explained by the fact that experimental investigation of the phenomena had never been previously undertaken. In study 5, we proposed that individual differences in the impact of top-down processes on elementary visual functions may determine the degree to which an amputee shows obstacle shunning or obstacle tolerance. To test this hypothesis, we borrowed a paradigm from cognitive science, i.e., the apparent motion perception task involving human body parts as stimuli (Shiffrar & Freyd, 1990). In this task, illusory visual perception of an actor's limb movements can be induced by the consecutive flashing of pairs of photographs depicting two limb positions. In healthy participants, the perceived trajectory of the apparent motion (depicted from two photographs showing a limb as once to the right and once to the left of a solid object) depends on the flash rate: during rapid flashing, the perceived trajectory is visually guided and appears to move straight through the object. A violation of the law of impenetrability of two solid objects (Hellman et al., 2015) then occurs, and obstacle tolerance can be experienced even by intact individuals. A slow flash rate, however, changes the perceived trajectory in such a way that the limb is seen to move around the object, and is therefore presumably more under sensorimotor guidance (Shiffrar & Freyd, 1990; Stevens et al., 2000). Twelve unilateral lower-limb amputees with phantom sensations (6 with obstacle shunning and 6 with obstacle tolerance) and 14 non-amputees were tested with this task. Amputees were only eligible if they had a unilateral lower limb amputation and experienced phantom limb sensations in everyday life.

Methods. Stimulus pairs comprising one picture with the target limb in front of a solid object and another with the limb behind the same object were presented alternately with varying stimulus duration (SD) and inter-stimulus-interval (ISI) at either long or short SOA. Four stimulus categories were included, based on: the limb depicting apparent motion (legs/arms), laterality of the limb (left/right), and object valence (threatening/neutral).

Results and implication. Amputees with obstacle shunning were more likely to perceive the missing body part as going through a solid object. The performance of amputees with obstacle tolerance did not differ from those of intact individuals, suggesting that when the phantom tolerates an object's presence, it imparts the same biomechanical constraints as an intact limb. These findings highlight the amputees' phantom limb motor schema, and how they interact with objects in the environment in everyday situations might be related to their apparent motion perception. This might open new tools for diagnostics and rehabilitation, considering that current assessments of disorders of the bodily self are exclusively based on self-reports and explicit measures.

Strengths and limitations. While this is the first report that characterized obstacle shunning and obstacle tolerance on an implicit level, the number of tested participants is relatively low (12 amputees and 14 controls). Despite the fact that the mixed model procedure we used allowed for modeling more than 4000 observations across all the participants, while adjusting for within-subject and within-group dependence, future studies should recruit more participants. Another critical issue concerns the apparent motion perception task we used as engaging the observer's sensorimotor system. In the present study, this was inferred exclusively from behavior. However, should researchers and clinicians desire to implement this task to analyze the disorders of body representation, they should first ensure that in this task, the observer’s limb sensorimotor representations are activated. The next session of the general discussion treats this issue in detail.

Sensorimotor representations underlying visual apparent motion perception

The debate in the literature has emphasized two main hypotheses to account for the SOA effect observed in study 5, and for the way implicit and intuitive physical notions exert their influences on the illusory perception in a top-down manner by modifying the visually perceived motion path. According to the motor hypothesis, the perception of plausible body motions that adhere to the law of impenetrability is grounded in the observer's sensorimotor representations acquired through motor execution. In favor of this hypothesis, Stevens et al. (2000) demonstrated that the perception of feasible biological motions was accompanied by the recruitment of the superior parietal and the primary motor cortices, i.e., regions where the repertoire of possible movements is represented. Moreover, Moseley & Brugger (2009) observed in 7 amputees that training a phantom limb to execute impossible movements induced the illusory perception of implausible movements, regardless of the SOA. This effect was specific for the situation in which the actor's limb and the amputee’s phantom limb matched. The visual hypothesis, instead, states that illusory perceptions of plausible body motions concern exclusively the activity of an observer's visual system and involve the visual representation of possible movements acquired during a history of visual-perceptual experiences. Vannuscorps & Caramazza (2016) compared the illusory perceptions of upper limb movements of 5 individuals born without an upper limb to those of able-bodied controls and found no significant differences. They concluded that the deprivation of the somatosensory schema does not affect the perceived motion trajectories. Previous studies in this specific field implemented only behavioral approaches, except for one single study using Positron Emission Tomography (PET) (Stevens et al., 1999), which nevertheless represents a correlational method. To address this debate in the literature, we conducted a transcranial direct current stimulation (tDCS) study (Saetta et al., in preparation). We investigated whether the transient reduction of the primary motor cortex's excitability would bias the judgment towards a visually-guided perception even for stimulus pairs with slow flash rates, which would be further evidence supporting the motor hypothesis. In an apparent motion perception task, we presented 24 able-bodied participants with body parts that could either be perceived as moving through or around physical objects. Twelve participants were assigned to the real stimulation condition where a cathodal tDCS (1 mA, 20 min) was applied over the motor cortex (C3), and twelve received sham stimulation (1mA, 15 sec). We found that cathodal tDCS affected the perceived trajectories in the expected direction, increasing the likelihood that participants would perceive the non-feasible movement trajectory. This effect was more pronounced for stimuli presented with a slow flash-rate. With the implementation of tDCS as a causative method, our results provide clear support of the motor hypothesis of apparent limb motion perception. Furthermore, they encourage the use of similar paradigms for exploring, on an implicit level, the visuo-motor properties of phantom limbs in amputees during the interaction with external objects.

An evidence-based neurocognitive model for the bodily self

The general discussion concludes with the proposal of a comprehensive neurocognitive model, encompassing own findings across the experiences of the disunity of body and self that I explored in my thesis.

According to the model I propose, the healthy binding of body and self (i.e., a coherent bodily self where the felt and visible limbs' boundaries match) inevitably relates to a smooth interplay between four mutually interacting levels of bodily processing (here for explanatory reasons listed from the lowest to the highest one):

1. Functional connectivity of the primary area containing the limb sensorimotor representation.

2. Limb multisensory integration relying on the functional connectivity and gray matter characteristics of dedicated multimodal cortical hubs.

3. Limb self-attribution relying on efficient interhemispheric communication.

4. Implicit (body schema) and explicit (body image) central representations of body size, shape, location, and physical composition scaffolded by distributed networks, in which the right superior parietal lobule plays a fundamental role.

1. The results of studies 1 and 2 converge in outlining that the efficient anchoring of the limb sensorimotor representation to different largescale networks is a key process for the feeling that a limb belongs. In study 1 we observed in BID individuals reduced connectivity of the right paracentral lobule, which hosts the sensorimotor representation of the disowned limb, i.e., the left leg. In study 2, we identified a lack of functional connectivity of the disowned hand's sensorimotor network as a distinctive neural signature of somatoparaphrenia. While the minimal common denominator between BID and somatoparaphrenia, is the limb disownership, phantom limb sensations (studies 4-5) are characterized by the feeling as if the amputated limb is "overly present". Interestingly, a recent study (Bramati et al., 2019) recruiting amputees with *non-painful* phantom limb sensations found the opposite

functional connectivity pattern compared with those observed in BID and somatoparaphrenia. This pattern consisted of an increased intra-hemispheric functional connectivity of the sensorimotor and premotor areas contralateral to the amputation. Remarkably, the strength of the approach they used was to exclude amputees with painful phantom limb sensations. This allowed for dissecting the cortical reorganization processes due to the persistence of the body's neural representation from those strictly related to pain (Makin et al., 2013). Taken as a whole, own and other's findings suggest that the functional connectivity pattern might be exploited as neuromarkers for specific feelings of disunity of the body and the self.

2. Multisensory integration refers to the process of binding unimodal visual, tactile, vestibular, impressions from a limb together, allowing a coherent central representation of the body. Studies 1 and 2 identified the alterations of two key "integrators" in the brain, predicted from the literature as potential candidates for limb disownership (see results and implication section of study 1 and study 2 in the general discussion). The first integrator was the left ventral premotor cortex, found atrophic in BID (study 1). The second was the pars opercularis of the right inferior frontal gyrus, found structurally and functionally altered in somatoparaphrenia (study 2). Interestingly, no lesions of these two key areas were observed in the case of asomatognosia (study 3). The evidence produced in this thesis is compatible with the view that the key multisensory integration might be associated explicitly with limb ownership but not for the feeling of absence of a visible limb.

3. Limb misattribution to another person is the productive component that distinguishes somatoparaphrenia (study 2) from all the other disorders of body ownership (study 1) and the bodily self in general (studies 3-5) examined in the thesis. In particular, limb misattribution can be ascribed, at least to some extent, to the loss

of the functional coupling (i.e., negative correlation) between the activity of the pars opercularis of the right inferior frontal gyrus in the right hemisphere and the activity of what we identified as the "narrator" in the left hemisphere (localized in Broca's area and the left temporo-parietal junction).

4. A proof of the existence of central body representations, relatively stable and detached from the sensory input, at least partly, comes from the evidence that anesthetizing a limb does not result in the phenomenal experience of the limb having faded (Melzack & Bromage, 1973). Body schema and body image are respectively referred to as implicit and explicit central body representations. The first is a postural model that guides action execution. The latter regards the conscious appraisal of physical appearance. As we observed in studies 2 and 3, somatoparaphrenia and asomatognosia are typically framed as body schema disorders. At the same time, BID and phantom limb sensations are purportedly disorders of body image, as observed in study 1, studies 4-5, and recently by Longo (2020) in his commentary to study 1). However, as noted by Cuzzolaro, (2018) the definitions of body schema and body image are often used interchangeably. Independent from whether the affected central body representation was implicit or explicit, in the present thesis, I discovered that, across *all* the examined disorders, a specific involvement of the right superior parietal lobule (rSPL). This suggests its role as the predominant "container" of the central body representations among all the other hubs distributed in the brain. The rSPL was atrophic in BID (study 1), lesioned in somatoparaphrenia (study 2), and in asomatognosia (study 3). Furthermore, previous studies showed that lesions of the rSPL are capable of suppressing the experience of phantom limb sensation (Berlucchi & Aglioti, 1997) . Indirect evidence of the involvement of the rSPL in asomatognosia and phantom limb sensations might come from the behavioral observations offered in studies 3-5. Patients' abnormal performances in the two tasks could be related to

their clinical symptomatology. Since both the hand laterality task and the apparent motion perception task (Stevens et al., 2000) trigger the activation of the rSPL, one may speculate that altered performances might mirror alteration in rSPL. However, only future neuroimaging studies combining behavioral and fMRI tasks may support or refute this hypothesis.

This thesis's empirical approach was admittedly inclined to uncover the neural mechanisms of the bodily self's disorders and relate them to their extraordinary phenomenological experiences. However, I would like to conclude my doctoral thesis with the vital claim of considering nonlinear interactions of biological, psychological, and social factors in all these aberrant conditions. I believe that only an integrative, cross-disciplinary view that includes the brain, the mind, and the society as equally important levels of analysis will determine important advances in understanding and diagnosing complex neuropsychological disorder

SUMMARY

Our self is bound to the body and we feel rooted to it. The boundaries of our body, set by bone and flesh, constrain and provide the space where our self can reside. However, the general rule that these borders constrain the experience of our self may, in some cases, no longer apply. In my thesis I provided both a neural and phenomenological account of the borderlands of the experience of having a body. Two aims motivated this thesis: i) I wanted to shed new light on the neural aspects underlying the bodily self, ii) I wanted to offer new tools for the clinical assessment and the experimental investigation of its disorders. Studies **1-2** were more focused on the first aim, **studies 4-5** on the second.

Study 1 explored the neural correlates of Body Integrity Dsyphoria (BID), a developmental disorder where a limb is felt as non-belonging. Persons with BID deny the limb ownership and seek its amputation to paradoxically "*feel more complete*". Results show that limb ownership depends on (1) the functional connectivity of the brain area containing its primary sensorimotor representation and (2) the structural and functional integrity of areas representing the body as a whole.

Study 2 mapped the dysfunctional networks in somatoparaphrenia, an acquired condition where a controlesional paralyzed limb is experienced as non-belonging and misattributed to someone else. Results link the limb misattribution to the activity of crucial hubs for integrating the multimodal signals of the affected hand. Furthermore, they provide the first direct evidence supporting the "left narrator model", proposed by Halligan et al. (1995), according to which the confabulations of SP are due to hemispheric disconnection.

Study 3 described a case of asomatognosia where a following a brain injury, the controlesional limb is felt as if it ceased to exist. We described a case and offered: i) a rigorous definition of asomatognosia for the clinical and scientific literature, ii) a structured interview to use to separate core and associated symptoms, iii) a computerized task to tap into the characteristics of sensorimotor representations underlying the limb felt as absent and capture phenomenological elements of a case by chronometric means. Results suggest that asomatognosia is characterized by alterations of the body schema and encourage the future of the provided materials.

Study 4 explored phantom limb sensations, i.e. postural and motor sensations felt in the extracorporeal space beyond the anatomical border as a "ghostly" products of the mind. The study hinged on the clinical assessment of phantom limb sensations and on gathering new experimental paradigms to capture individual differences in these sensations. We shared with the scientific community datasets containing: i) quantitative and qualitative data on phantom limb sensations collected during a 2 h clinical interview; ii) multimodal data (gaze, surface electromyography, accelerometry, and behavioral) on eye-phantom coordination, iii) multimodal data on the way a phantom interact with solid objects. Results confirm the usability of the data for further hypothesis testing.

Study 5 characterized an under-investigated property of the phantom limb concerning its interaction with physical matter co-located in the space: the bending back or disappearance (i.e., obstacle shunning) or its being felt within the physical matter (i.e., obstacle tolerance). We used an apparent motion perception task. The illusion of apparent motion of human limbs involves the perception that a limb moves through or around an object, depending on the stimulus onset asynchrony (SOA) for the two images. Results highlighted that the amputees' phantom limb motor schema, and how they interact with objects in the environment in everyday situations might be related to their apparent motion perception. This might open new tools for diagnostics and rehabilitation.

Together, the data illustrated the multifaceted nature of the bodily self and tentatively outlined how contributing factors, from neurological to social, could be mapped to the brain and be reflected in behavior, and how they may be employed for both clinical and research purposes.

SOMMARIO

l nostro sé è legato al nostro corpo. I confini del nostro corpo, delimitati da carne e ossa, forniscono lo spazio entro cui il nostro sé possa risiedere. Tuttavia la regola generale secondo cui questi confini limitano l'esperienza del nostro sé non si applica in alcuni casi. Nella mia tesi ho fornito un resoconto sia neurale che fenomenologico di alcuni di questi casi. Due obiettivi hanno motivato questa tesi: i) fornire nuove evidenze sugli aspetti neurali alla base del sé corporeo, ii) offrire nuovi strumenti per la valutazione clinica e l'indagine sperimentale dei suoi disturbi. Gli studi 1-2 sono particolarmente incentrati sul primo obiettivo, gli studi 4-5 sul secondo.

Lo **studio 1** ha esplorato i correlati neurali del disturbo denominato Body Integrity Dsyphoria (BID), un disturbo dello sviluppo in cui le persone affette riferiscono che un arto sano non appartenga al proprio corpo. Le persone con BID richiedono l'amputazione di tale arto paradossalmente per "sentirsi più completi". I risultati mostrano come l'ownership di un arto dipenda (1) dalla connettività funzionale dell'area cerebrale contenente la rappresentazione sensorimotoria primaria dell'arto interessato dal disturbo e (2) dall'integrità strutturale e funzionale delle aree contenti la rappresentazione del corpo nel suo insieme.

Nello **studio 2** abbiamo mappato i network cerebrali disfunzionali alla base della somatoparafrenia, una condizione acquisita in cui l'arto paralizzato controlesionale viene esperito come non appartenente al proprio corpo e attribuito erroneamente ad un'altra persona. I risultati collegano l'errata attribuzione dell'arto all'attività di centri cerebrali in cui i segnali multimodali della mano interessata dal disturb vengono integrati. Inoltre forniscono la prima prova diretta a supporto del "modello narratore sinistro" proposto da Halligan et al. (1995), secondo cui le confabulazioni tipiche dei pazienti con somatoparafrenia sono dovute ad una disconnessione interemisferica.

Lo **studio 3** ho presentato un caso di asomatognosia, una condizione neuropsicologica in cui a seguito di una lesione cerebrale, gli arti controlesionali sono percepiti come se avessero cessato di esistere. In questo studio, abbiamo descritto un caso particolare e offerto: i) una definizione rigorosa di asomatognosia utile a fini di ricerca e clinica, ii) un'intervista strutturata da utilizzare per discernere i sintomi caratteristici da quelli meramente associati, iii) un compito computerizzato per esplorare lo *status quo* delle rappresentazioni sensorimotorie dell' arto "assente". Tale compito è in grado di cogliere i peculiari aspetti fenomenologici di un caso clinico attraverso l'analisi dei tempi di reazione. I risultati dello studio suggeriscono come l'asomatognosia sia caratterizzata da specifiche alterazioni dello schema corporeo e incoraggiano il futuro utilizzo dei materiali forniti.

Lo **studio 4** ha esplorato le sensazioni dell'arto fantasma, vale a dire sensazioni posturali e motorie avvertite nello spazio extracorporeo, oltre i confini anatomici del corpo, come prodotti "spettrali" della mente. Lo studio si è imperniato sulla valutazione clinica delle sensazioni dell'arto fantasma e sulla stesura di nuovi protocolli sperimentali per l'esplorazione delle differenze individuali nell'esperire tali sensazioni. Abbiamo condiviso con la comunità scientifica diversi dataset contenenti: i) dati quantitativi e qualitativi relativi alle sensazioni dell'arto fantasma raccolti durante un colloquio clinico della durata di circa 2 ore; ii) dati multimodali (sguardo, elettromiografia di superficie, accelerometria, e dati comportamentali) sulla coordinazione occhio-fantasma, iii) dati multimodali sul modo in cui l'arto fantasma interagisce con oggetti solidi. I risultati dello studio confermano l'usabilità dei dati contenuti nei dataset forniti per testare nuove ipotesi di ricerca.

Lo **studio 5** ha caratterizzato una proprietà peculiare dell'arto fantasma riguardante la sua interazione con oggetti solidi co-locati nello spazio: il piegarsi all'indietro o la scomparsa (obstacle shunning) o il suo essere esperito come se fosse all'interno dell'oggetto (obstacle tolerance). In questo studio abbiamo utilizzato un compito di percezione del movimento apparente. L'illusione del movimento apparente degli arti umani consiste nella percezione che un arto si muova attraverso o intorno a un oggetto, a seconda di come vengano lampeggiate due immagini statiche raffiguranti due diverse posizioni dell'arto rispetto all'oggetto. I risultati hanno evidenziato come lo proprietà motorie dell'arto fantasma e il modo in cui gli amputati interagiscono con gli oggetti nell'ambiente nelle situazioni quotidiane siano correlate alla loro percezione del movimento apparente. I risultati potrebbe ispirare la creazione di nuovi strumenti per la diagnostica e la riabilitazione.

Nel loro insieme, i dati presentati in questa tesi hanno illustrato la natura multiforme del sé corporeo e hanno delineato i fattori alla sua base, sia neurologici che sociali. Inoltre ha mostrato come tali fattori possano essere mappati nel cervello e riflettersi nel comportamento dell'individuo, e come la loro analisi possa essere particolarmente utile per scopi sia clinici che di ricerca.

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Second University of Naples – Department of Psychology, CS (Italy)
Thesis Title: "*Body Integrity Identity Disorder (BIID): a neurofunctional Resting State fMRI Study*"
Supervisors: Profs. Gabriella Bottini, Dario Grossi
Final mark: 110/110 Summa cum Laude

Bachelor's Degree in Psychology – 24/10/2011
University of Naples "Federico II" - Department of Humanistic Studies, Naples (Italy)
Thesis Title: *"Classical Cognitive science versus experimental neurosciences comparison: from the concept of affordance to the embodied cognition"*
Supervisor: Prof. Orazio Miglino
Final Mark: 110/110 cum Laude

Scientific High School Degree – 04/07/2008
Liceo Scientifico Statale "Vincenzo Cuoco", Naples (Italy)

Research and Clinical Employment

Visiting Research Fellow – 01/08/2019 to 24/09/2020
University of Utrecht – Department of Experimental Psychology, Heidelberglaan 1 3584 CS, Utrecht (The Netherlands)
Topic: The role of the motor cortex in the body perception
Methods: Behavioral tasks, tDCS, TMS
Supervisors: Profs. Chris Dijkerman, Dr. Dennis Schutter

Volunteer as Clinical Neuropsychologist – 01/02/2016 to 31/06/2019
Department of Neurology, Frauenklinikstrasse 26 CH-8091, Zurich

- Neuropsychological assessment with ad hoc designed computerised tasks

Soft Skills

- Result Driven
- Excellent team work skills
- Inclined to work in multicultural environment
- Trombone player

Post Master's degree Research Internship – July 2015 – January 2016
University of Milano-Bicocca – Department of Psychology
Piazza dell'Ateneo Nuovo, 1, 20126 Milan (Italy)

- Behavioural and neuroimaging data collection and analyses

Tutors: Profs. Eraldo Paulesu and Manuela Berlingeri

Post Master's degree Clinical and Research Internship – January 2015 – June 2015
University of Pavia – Department of Brain and Behavioral Sciences
P.zza Botta 11 27100, Pavia (Italy)

- Neuropsychological assessment in clinical populations

Tutors: Profs Gabriella Bottini and Martina Gandola

Grants, Multidisciplinary and International Collaborations

- **PhD Fellowship** - Sinergia Project #410160837 Myo-electricity, gaze and artificial intelligence for neurocognitive examination and prosthetic in transradial hand amputees (MeganePro). SNF
- **Visiting Researcher Fellowship** – Doc.Mobility #181383. SNF

Teaching activities

- **Lecturer at the University of Zurich**, Faculty of Biology, Module BIO 404 for 5 academic years in a row, 2016-2020
  Description: Block course (30 teaching hours per year) for the Bachelor degree program in *Biology*. Student learnt to perform a scientific experiment from the scratch and were involved in critical literature review and in testing healthy volunteers
  Total teaching hours in 5 years: 150. Number of supervised students: 22
- **External Lecturer at University of Pavia (Italy),** MSc in Psychology, Neuroscience and Human Sciences, Spring Semesters 2019, 2020
  Description**:** Seminars (12 hours per year) for the course "Clinical Neuropsychology" (M-PSI/02) on the topics: methods of investigation in cognitive and clinical neuropsychology (with a particular focus on resting-state fMRI and fMRI); classification of neuropsychological disorders

Scientific reviewing activities

- Reviewer for the journal "*Cortex*"
- Reviewer for the journal "*Brain Connectivity*"
- Assisting Prof. Peter Brugger in reviewing papers from different top-ranked journals

Job-related skills

- Relevant expertise in implementation of brain imaging techniques: fMRI with active tasks, resting-state fMRI, VBM, eye tracker
- Relevant expertise in the neuromodulation of the brain activity: tDCS and TMS
- Relevant expertise in the design of online experiments and big data manipulation
- Excellent knowledge of the main neuropsychological and cognitive tests

Publications List

Published peer-reviewed articles

Saetta, G., Hänggi, J., Gandola, M., Zapparoli, L., Salvato, G., Berlingeri, M., Paulesu, E., Bottini, G., & Brugger, P. (2020). Neural correlates of body integrity dysphoria. *Current Biology.* 30, 2191–2195

Saetta, G., Cognolato, M., Atzori, M., Faccio, D., Giacomino, K., Mittaz, Hager, A.-G., Tiengo, C., Bassetto, F., Müller, H., & Brugger, P. (2020). Gaze, behavioral and clinical data for phantom limbs after hand amputation from 15 amputees and 29 controls. *Nature: Scientific Data*, 7(1), 1-14.

Saetta, G., Brugger, P., Schrohe, H., & Lenggenhager, B. (2019). Putting Yourself in the Skin of In- or Out-Group Members: No Effect of Implicit Biases on Egocentric Mental Transformation. *Frontiers in Psychology*, 10.

Saetta, G., Grond, I., Brugger, P., Lenggenhager, B., Tsay, A. J., & Giummarra, M. J. (2018). Apparent motion perception in lower limb amputees with phantom sensations: “Obstacle shunning” and “obstacle tolerance.” *Cortex*, 104, 220–231.

Zapparoli, L., **Saetta, G.**, De Santis, C., Gandola, M., Zerbi, A., Banfi, G., & Paulesu, E. (2016). When I am (almost) 64: The effect of normal ageing on implicit motor imagery in young elderlies. *Behavioural Brain Research*, *303*, 137-151.

Gregori, V., Cognolato, M., **Saetta, G**., Atzori, M., Consortium, T. M., & Gijsberts, A. (2019). On the Visuomotor Behavior of Amputees and Able-Bodied People During Grasping. *Frontiers in Bioengineering and Biotechnology*, 7.

Gandola, M., Zapparoli, L., **Saetta, G**., De Santis, A., Zerbi, A., Banfi, G., Sansone, V., Bruno, M., & Paulesu, E. (2019). Thumbs up: Imagined hand movements counteract the adverse effects of post-surgical hand immobilization. Clinical, behavioral, and fMRI longitudinal observations. *NeuroImage: Clinical*, 23, 101838.

Cognolato, M., Gijsberts, A., Gregori, V., **Saetta, G**., Giacomino, K., Mittaz, Hager, A.-G., Gigli, A., Faccio, D., Tiengo, C., Bassetto, F., Caputo, B., Brugger, P., Atzori, M., & Müller, H. (2020). Gaze, Visual, Myoelectric, and Inertial Data of Grasps for Intelligent Prosthetics. *Nature: Scientific Data.*

Gandola M., Bruno, M., Zapparoli, L., **Saetta, G**., Rolandi, E., De Santis, A., Banfi, G., Zerbi, A., Sansone, V., Paulesu, E. (2017). Functional brain effects of hand disuse in patients with trapeziometacarpal joint osteoarthritis: executed and imagined movements. *Experimental Brain Research*, *235*(10), 3227–324.

Cognolato, M., Graziani, M., Giordaniello, F., **Saetta, G**., Bassetto, F., Brugger, P., … Atzori, M. (2017). Semi automatic Training of an Object Recognition System in Scene Camera Data Using Gaze Tracking and Accelerometers. In *Computer Vision Systems* (pp. 175–184). Springer, Cham.

Huynh, V., Scherf, A., Bittner, A., **Saetta, G.**, Lenggenhager, B., & Beckerle, P. (2018). Design of a wearable robotic hand to investigate multisensory illusions and the bodily self of humans. ISR 2018; *50th International Symposium on Robotics*, 1–6.

Giordaniello, F., Cognolato, M., Graziani, M., Gijsberts, A., Gregori, V., **Saetta, G.,** … Atzori, M. (2017). Megane Pro: Myo-electricity, visual and gaze tracking data acquisitions to improve hand prosthetics. In 2017 *International Conference on Rehabilitation Robotics (ICORR)* (pp. 1148–1153).

Articles under review

Saetta, G., Paulesu, E., Sberna, M., & Berlingeri, M. (under review). The rostro-caudal gradient of the hippocampus: Resting-state functional connectivity evidence.

Saetta, G., Michels, L., & Brugger, P. (under review). Where in the brain is "the other's" hand? Mapping dysfunctional neural network in somatoparaphrenia.

Saetta, G., Zindel-Geissler, O., Stauffacher, F., Serra, C., Vannuscorps, G., & Brugger, P (accepted pending minor revisions). Asomatognosia: Structured interview and assessment of visuo-motor imagery.

Selected Press-releases

CNN – Understanding the rare condition that makes people want to amputate their own limbs – https://edition.cnn.com/2020/05/07/health/body-integrity-dysphoria-wellness/index.html

Cell-Press News – The feeling a limb doesn't belong is linked to lack of brain structure and connection - https://medicalxpress.com/news/2020-05-limb-doesnt-linked-lack-brain.html?fbclid=IwAR3JeWnNC9P-Tw1nwAaJYkndoSjlvPPT0StJzfkfXuPQEaHC4jkjxA4A6HA

ORF – Wenn der Kopf den Körper ablehnt - https://science.orf.at/stories/3200720/

Spektrum – Warum sich manche Menschen eine Amputation wünschen - https://www.spektrum.de/news/neue-forschungen-zur-body-integrity-dysphoria-stoerung/1733584

Scientific American (in Arabic) - مرضى «متلازمة نزاهة الهوية الجسدية» يعانون خللًا في بنية المخ – https://www.scientificamerican.com/arabic/articles/news/feeling-limb-does-not-belong-linked-to-lack-of-brain-structure/

Invited talks

Saetta G., The neural basis of limb ownership and body integrity. Guest Colloquia of the Department of Experimental Psychology, University of Utrecht (The Netherlands). 6th of February 2020.

Saetta G., The neural basis of limb ownership. An investigation in Body Integrity Dysphoria and Somatoparaphrenia. Psychology Department, Heriot Watt University (United Kingdom). 30th of April 2019.

Saetta G., A dangerous desire: neuroanatomical and neurofunctional characterisation of Body Integrity Dysphoria. Cognitive Ageing and Impairment Neuroscience Center. University of South Australia (Australia), 16th of November 2018.

In the cover:
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